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[Authors]. [Abstract Title]. Program No. XXX.XX. 2018 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2018. Online.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Support: BBSRC EASTBIO PhD Studentship

Title: Understanding the role of 16p11.2 CNV genes in human cerebral corticogenesis

Authors: *S. MORSON, Y. YANG, D. J. PRICE, T. PRATT
The Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: The process of the brain developing from a single fertilised cell to the most sophisticated known organ requires precise spatial and temporal control to produce the required brain size and architecture. A particular region of interest is the cerebral cortex, responsible for higher functions such as language, reasoning and conscious thought. Its expansion in size and complexity from smaller mammals (such as mice) to humans is thought to give rise to our higher functions. However a caveat of this increased complexity is the increased challenge of generating such a complex structure, and the potential for subtle changes during neurodevelopment to manifest in neurodevelopmental disorders, such as Autism Spectrum Disorders (ASD).
The 600kbp 16p11.2 CNV encompasses 29 genes and its heterozygous duplication (dup) or deletion (del) is implicated in around 1% of ASD cases, with many patients suffering macrocephaly (del) or microcephaly (dup) indicating early neural proliferation defects. Given the vast heterogeneity of ASD this is a significant proportion making this region a promising area of study to understand how genetic dysregulation during critical pre-natal neurodevelopment can contribute to the ASD phenotype.
Using *in silico* analysis of human fetal scRNA-seq data to identify candidate genes we present highly novel data showing the *in vivo* expression pattern of genes enriched during neural proliferation during human corticogenesis. We describe their role in regulating proliferation to understand how their dysregulation may underlie the patient phenotype.
In parallel, we show data from our studies using hiPSCs derived from 16p11.2 del patients to elucidate the complex molecular changes early in neurogenesis that may underlie the phenotype of this CNV, with the long term goal of culturing cerebral organoids. This allows us to test our hypothesis that the 16p11.2 CNV genes play a vital role in human neurogenesis.

Disclosures: S. Morson: None. **Y. Yang:** None. **D.J. Price:** None. **T. Pratt:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIA Grant 1R01AG053382
NIA Grant 1R01AG055797
UCSF Anatomy Department
UCSF Office of the Chancellor

Title: Ogt regulates adult hippocampal neurogenesis and cognition

Authors: *C. W. WHITE, III[1], X. FAN[2], E. WHEATLEY[1], G. BIERI[3], S. A. VILLEDA[2]
[1]Developmental and Stem Cell Biol., [2]Anat., Univ. of California, San Francisco, San Francisco, CA; [3]Stanford Univ., Menlo Park, CA

Abstract: Adult hippocampal neurogenesis, the process by which new neurons are generated in the adult hippocampus, provides a significant source of cellular plasticity in the adult brain. Within the dentate gyrus subregion, neural progenitor cells (NPCs) undergo rounds of division and maturation, ultimately giving rise to functional neurons that integrate into existing hippocampal circuitry. Decreased adult neurogenesis is commonly observed alongside impaired cognitive function, in conditions such as neurodegenerative disease and aging. Given the prevalence of these conditions, it is critical to understand the mechanisms regulating the self-renewal and differentiation of adult NPCs. One potential mediator of these processes is the post-translational modification O-linked β-N-acetylglucosamine (O-GlcNAc). Previously implicated in the context of regulation of gene expression in embryonic stem cells, the catalytic enzyme responsible for addition of this modification, O-GlcNAc transferase (Ogt), has also been shown to be essential for both embryonic stem cell and neuronal survival. Interestingly, the roles of O-GlcNAc and Ogt have not yet been explored in NPCs. Here we report that Ogt regulates adult hippocampal neurogenesis, and associated cognitive processes. Using an in vitro lentiviral-mediated RNAi approach, we demonstrate that abrogating Ogt expression in primary NPCs impairs self-renewal and proliferation. Using a complementary in vivo lentivirus-mediated RNAi approach resulted in a marked decrease in NPC proliferation following Ogt knockdown in the adult dentate gyrus. To gain further mechanistic insight at a cell-type specific level in vivo, we utilized a temporally controlled adult NPC-specific conditional knockout mouse model. Loss of Ogt in adult NPCs resulted in decreased levels of adult neurogenesis accompanied by impairments in spatial learning and memory, and associative fear memory. Taken together, this work identifies Ogt as a novel regulator of adult NPC function, and posits O-GlcNAcylation as a

potential therapeutic target for ameliorating neurodegenerative- and age-related loss of neurogenesis and associated cognitive decline.

Disclosures: C.W. White: None. **X. Fan:** None. **E. Wheatley:** None. **G. Bieri:** None. **S.A. Villeda:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: the Zhejiang Provincial Natural Science Foundation of China (LY17C090007)
the National Natural Science Foundation of China (31271176)

Title: HDAC3 differentially regulates the proliferation of two progenitor pools by Wnt/β-catenin signaling in the developing tectum

Authors: *W. SHEN[1], J. GAO[2], Z. GUO[1], L. ZHENG[1], N. DING[1], Y. LIAO[1]
[1]Col. of Life and Envrn. Sci., [2]Hangzhou Normal Univ., Zhejiang, China

Abstract: It is known that radial glial cells (RGs) are one of the major progenitor cells in the developing Xenopus tectal brain. Our previous data have shown that a majority of BLBP-positive RGs are BrdU+ progenitor cells. Visual experience-dependent proliferation of RGs is selectively mediated by histone deacetylase 1/3 (HDAC1/3) but not HDAC2 in the developing brain. However, the classification of progenitor cells is not fully determined in the developing optic tectum. We immunostained the whole tectal brain at different developmental stages and find that SOX2+ and BLBP+ progenitor cells are specifically distributed along the ventricles. In particular, we first find that there is a large cluster of SOX2+ and BLBP- cells located in the pretectum, which are SOX6- and SOX9- at stage 47. We previously have shown that RGs are BrdU+ progenitor cells by bath incubation of BrdU. Interestingly, the SOX2+ cells in pretectum can only be labeled by brain injection of BrdU. These data indicate that there are two distinct progenitor pools existed in the developing tectal brain. The SOX2+ progenitor cells in pretectum and ventricle may play different roles in the brain development. To determine whether HDAC is involved in the proliferation of SOX2+ cells, tadpoles were exposed to a HDAC inhibitor (VPA). The number of SOX2+ cells is greatly increased in the ventricular layer while significantly decreased in the pretectum at stage 49 tadpoles. The histone of H3 acetylation at lysine 9 and H4 acetylation at lysine 12 were consistently increased. To determine whether SOX2+ cells are regulated by visual experience, tadpoles were exposed to visual deprivation (VD) for 2 days. We find that the proliferation of SOX2+ cells are dramatically decreased by VD in the pretectum while gradually increased in the ventricle. Furthermore, the expression of SOX2 cells in the

pretectum is significantly decreased in response to visual deprivation by Western blot. In particular, SOX2 are colocalized with β-catenin only in the pretectum but not in the ventricle. Knockdown of SOX2 decreases the expression of HDAC3 and β-catenin while knockdown of β-catenin also decreases the expression of HDAC3 and SOX2. These data suggest that visual experience dependent proliferation of SOX2+ cells is differentially regulated by SOX2, β-catenin and HDAC3 signaling.

Disclosures: W. Shen: None. **J. Gao:** None. **Z. Guo:** None. **L. Zheng:** None. **N. Ding:** None. **Y. Liao:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: 31425011
MH094589

Title: Dlx1/2 promote olfactory bulb interneuron generation through activating Sp8/9 expression

Authors: *T. GUO, H. DU, Z. YANG
Fudan Univ., Shanghai, China

Abstract: Generation of olfactory bulb (OB) interneurons requires neural stem/progenitor cell proliferation, specification and differentiation, and interneuron migration and maturation. Here, we show that the homeobox transcription factors *Dlx1/2* are required for the generation of all OB interneurons. In *Dlx1/2* constitutive null mutants, GSX2-expressing (+) and $ASCL1^{+}$ progenitors in the dorsal lateral ganglionic eminence (dLGE) fail to generate $Sp8/9^{+}$ OB interneurons, whereas they appear to transform toward immature undifferentiated medium spiny neuron-like cells. In adult *Dlx1/2* conditional mutants (hGFAP-Cre; $Dlx1/2^{F/-}$), $GSX2^{+}$ and $ASCL1^{+}$ neural progenitors in the subventricular zone generate neuroblasts that fail to express SP8 and SP9. Overexpression of DLX1/2 in neural progenitors of the E14.5 mouse neocortex led to generation of immature OB interneurons in the E18.5 cortex that express *Sp8/9*, *GAD1*, *Arx*, *Etv1*, *Pbx3*, *Tshz1* and *Prokr2* expression. Thus, we propose that DLX1/2 promote OB interneuron development mainly through activating the expression of *Sp8/9*. This study, in combination with earlier studies, presents a transcriptional regulatory network that controls the multistep process of OB interneuron development.
KEY WORDS: Dlx1; Dlx2; Gsx2; Ascl1, Sp8; Sp9*;* olfactory bulb; interneuron.

Disclosures: T. Guo: None. **H. Du:** None. **Z. Yang:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: Ecole de Neurosciences Paris Ile de France
BioPsy Labex
ANR-13-BSV4-0008-01
ANR-16-CE16-0011-03
Fondation Bettencourt Schueller
EU-HEALTH-2013, DESIRE, No 60253
JTC 2015 Neurodevelopmental Disorders

Title: Eml1 is involved in primary cilium formation at early stages of cortical development

Authors: *A. UZQUIANO[1,2], D. ROMERO[1,2], A. HOULLIER[1,2], F. DINGLI[3], G. ARRAS[3], D. LOEW[3], C. DIAZ-CIFUENTES[1,2], N. BAHI-BUISSON[4,5], F. FRANCIS[1,2]
[1]Inst. Du Fer A Moulin, Inserm U839, Paris, France; [2]Sorbonne University, Univ. Pierre et Marie Curie, Paris, France; [3]Inst. Curie, PSL Res. University, Ctr. de Recherche, Lab. de Spectrométrie de Masse Protéomique, Paris, France; [4]Paris Descartes - Sorbonne Paris Cité University, Imagine Inst., Paris, France; [5]Inserm U1163, Embryology and Genet. of Congenital Malformations, Paris, France

Abstract: Subcortical heterotopia (SH) is a cortical malformation characterized by the presence of mis-localized neurons beneath the normal cortex within the white matter. This pathology is associated with intellectual disability and epilepsy. The microtubule-associated protein EML1/Eml1 was found mutated in three families presenting this disorder (Kielar et al., 2014, Shaheen et al., 2017), as well as in the heterotopic cortex (*HeCo)* mouse, which is a model for SH. At early stages of corticogenesis, abnormally positioned neuronal progenitors were found cycling outside the proliferative ventricular zone (VZ) of the mutant cortex in the region where the heterotopia develops. In order to elucidate the mechanisms leading to ectopic progenitors, we study the *HeCo* VZ, focusing on apical radial glia (aRG) in this zone, the source of all other cortical progenitors. The *HeCo* mouse is hence a good model to study key features influencing neuronal progenitor behavior while shedding light on patho-mechanisms contributing to the heterotopia phenotype.
Using a variety of approaches (genetic tools, confocal and electron microscopy) we identified centrosome and primary cilia defects in *HeCo* aRG endfeet, which are also larger and less numerous at the mutant ventricular surface. Our data reveals that in Eml1 mutant conditions, primary cilia are shorter and often fail to protrude towards the ventricle, remaining basally

oriented. Ciliary anomalies associated with Eml1 mutations are supported by studies in patient fibroblasts, which also show a decrease in number and length of these organelles. Our converging data suggest an unprecedented role for Eml1 in primary cilium formation. Additionally, mass spectrometry (MS) analyses for Eml1 interacting partners point towards ciliary proteins. This combined approach followed by biochemical experiments has led us to confirm the interaction of Eml1 with the basal body-ciliary protein Rpgrip1l. Gene ontology analyses of MS data are guiding ongoing experiments to dissect the intracellular mechanisms by which primary cilia fail to properly form in Eml1 mutant conditions.

Disclosures: A. Uzquiano: None. **D. Romero:** None. **A. Houllier:** None. **F. Dingli:** None. **G. Arras:** None. **D. Loew:** None. **C. Diaz-Cifuentes:** None. **N. Bahi-Buisson:** None. **F. Francis:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant MH101188 to SCN
NIH Grant HL085794 to AFT
NIH Grant OD011107 to CNPRC
MIND Institute (IDDRC; U54 HD079125)

Title: Microglia interface with the mitotic neural precursor cells that line the surface of the lateral ventricles

Authors: *S. C. NOCTOR[1,2], H. SHEPHERD[7], J. KEITER[3], N. BARGER[1], A. KREUTZ[4], A. F. TARANTAL[5,6,8]
[1]Psych & Behavioral Sci., [2]MIND Inst., UC Davis, Sacramento, CA; [3]Ctr. for Neurosci., [4]Neurosci. Program, UC Davis, Davis, CA; [5]Pediatrics, UC Davis, Sacramento, CA; [6]Cell Biol. and Human Anat., UC Davis, Davis, CA; [7]Biol., Brigham Young Univ. - Idaho, Rexburg, ID; [8]Ctr. for Fetal Monkey Gene Transfer for Heart, Lung, and Blood Dis., California Natl. Primate Res. Ctr., Davis, CA

Abstract: Microglia contribute to the development of axonal pathways, synapse formation, cortical layer formation, and cell genesis. Yet, microglial cell functions in the prenatal brain are not fully understood. Microglia begin to colonize the cerebral cortex during prenatal development: in rat by embryonic day (E)13, and in rhesus monkey during the first trimester prior to 50 days gestation. Microglia do not initially distribute evenly throughout the cortex, as found in healthy adult cortex, but instead populate a few specific regions such as the cortical

proliferative zones. Furthermore, prenatal microglia in the cortex do not display the 'resting' morphology characteristic of healthy adult cortex, but exhibit distinct 'activated' morphological phenotypes that correlate with cell location in the proliferative zones. Microglia in the subventricular zone (SVZ) tend to exhibit an 'amoeboid' morphology - larger cell bodies with a few short, thick processes, while periventricular microglia have smaller soma and extend longer, thinner processes. We have found that microglia make extensive contacts with neural precursor cells (NPCs) throughout the proliferative zones. To shed light on microglial function in the proliferative zones we quantified the frequency and type of interactions between microglia and NPCs undergoing division at the surface of the ventricle, and NPCs dividing in the SVZ of prenatal rats and rhesus monkeys. In E19 rats fewer than 50% of NPCs dividing at the ventricle were contacted by periventricular microglia, but all periventricular microglia contacted multiple dividing NPCs. Periventricular microglia were more likely to contact the pial process of prophase and metaphase NPCs, and were more likely to contact the soma of anaphase and telophase NPCs. Similar interactions were observed in the gestation day 90 monkey, but a larger proportion of mitotic NPCs interacted with microglia in the rhesus monkey. Microglia interfaced with dividing NPCs in the SVZ of both species, but the number of microglia in the monkey SVZ was significantly higher. NPCs divide at the surface of the ventricle during forebrain development of all vertebrates, but the number of NPCs that divide away from the ventricle and in the SVZ varies significantly and is largest in species such as primates. Our data suggest that the number of periventricular and SVZ microglia across species correlates with the number of NPCs in the SVZ and that the distinct morphology of periventricular and SVZ microglia reflects different functional roles for these cells.

Disclosures: S.C. Noctor: None. **H. Shepherd:** None. **J. Keiter:** None. **N. Barger:** None. **A. Kreutz:** None. **A.F. Tarantal:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: KAKENHI JP16K07000

Title: Rac is required for the survival of cortical neurons

Authors: *K. KATAYAMA[1], Y. ZHENG[2]
[1]Dept. of Mol. Cell Biol. and Mol. Med., Wakayama Med. Univ., Wakayama, Japan; [2]Div. of Exptl. Hematology and Cancer Biol., Cincinnati Children's Hosp. Mrdical Ctr., Cincinnati, OH

Abstract: Rac1 is a member of Rho family small GTPases, and previous studies have shown that it plays important roles in various steps of neural development including neurogenesis, neuronal migration and neuritogenesis. However, these functions are mainly deduced from studies using cultured cells and its physiological roles in neural development still remain unclear. Previous studies showed that deletion of Rac1 in early neurodevelopmental stages caused severe microcephaly due to defective neurogenesis. In the present study, we deleted Rac1 using GFAP-Cre mice, which induces Cre/loxP recombination in neuronal cells from E13.5 to investigate the roles of Rac1 in later neurodevelopmental stages. Although cerebral cortices of Rac1;GFAP-Cre conditional knockout mice were slightly smaller than those of control mice, they grew up almost normally. To exclude the possibility that Rac3, a close homolog of Rac1 expressed in the nervous system, compensates the function of Rac1, we also deleted Rac1 in Rac3-null background. At birth, overall morphology of the Rac1/Rac3-deleted cerebral cortex was almost normal. However, soon after birth, cortical neurons lacking both Rac1 and Rac3 began to die by apoptosis. The cerebral cortex of Rac1;Rac3;GFAP-Cre conditional knockout mice became thinner as they grew up and the mice died before 3 weeks of age. Existence of either one allele of Rac1 or Rac3 could protect cortical neurons from apoptotic cell death. These results suggest that Rac plays a critical role in the survival of cortical neurons.

Disclosures: K. Katayama: None. **Y. Zheng:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI 16H05364
JSPS KAKENHI 15K15405
JSPS KAKENHI 16K19674

Title: Leukemia inhibitory factor signaling and STAT3 phosphorylation at Ser727 in fetal mouse brain development

Authors: *T. TSUKADA[1,2], H. SAKAGAMI[1], H. SHIMADA[1,3], S. TAKATA[2], H. SAKATA-HAGA[1], H. SHOJI[4], H. IIZUKA[2], T. HATTA[1]
[1]Anat., [2]Neurosurg., [3]Med. Sci., [4]Biol., Kanazawa Med. Univ., Ishikawa, Japan

Abstract: Leukemia inhibitory factor (LIF) in the fetal cerebrospinal fluid (CSF) may have a role in neural progenitor pool expansion and corticogenesis in the fetal rodent brain. Generally, LIF binds to specific receptors, LIFR and gp130, and subsequently signal transducer and activator of transcription 3 (STAT3) is activated by Janus kinase 2-mediated phosphorylation of

the Tyr705 site. It has been believed this activated STAT3 has an essential role in LIF–STAT3 signaling. STAT3 is known to have another phosphorylation site, Ser727, although the contributions of STAT3 phosphorylation at Ser727 to neurogenesis are unclear. In this study, the expression of LIF-related signal molecules and the phosphorylation of STAT3 were examined in the dorsal fetal mouse brain. Fetuses from C57BL/6J mice were collected during mid-gestational days. The concentration of LIF in the fetal CSF was measured using enzyme-linked immunosorbent assay and stained sections of fetal brain using antibodies for LIFR, gp130, and phosphorylation of STAT3 at Tyr705 and Ser727. The levels of phosphorylation of STAT3 at Tyr705 and Ser727 were also examined by Western blotting. The highest level of LIF in the fetal CSF was observed between 12.5 and 14.5 days post coitum (dpc). At 13.5 dpc, LIFR was expressed and gp130 was phosphorylated in the fetal brain. Sections indicated the phosphorylation of STAT3 at Ser727 but not that of STAT3 at Tyr705. In addition, Western blotting revealed phosphorylation of STAT3 at Ser727 but not at Tyr705 in the fetal brain. Considering the previous reports on the role of LIF in expanding neural progenitor pool, these results suggest that the phosphorylation of STAT3 at Ser727 plays a role in LIF-mediated neurogenesis independent of the phosphorylation of STAT3 at Tyr705 in fetal mouse brain.

Disclosures: T. Tsukada: None. **H. Sakagami:** None. **H. Shimada:** None. **S. Takata:** None. **H. Sakata-Haga:** None. **H. Shoji:** None. **H. Iizuka:** None. **T. Hatta:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Title: Cx43 as a marker gene of ependymal cells in the spinal cord of zebrafish embryo

Authors: *J. KIM, I.-H. JUNG
Chonnam Natl. Univ. Hosp., Gwangju, Korea, Republic of

Abstract: Objective: Ependyma is the simple ciliated epithelium that lines the ventricular surface of the central nervous system, and consists primarily of ependymal cells, one type of glial cells. Ependymal cells have cilia and microvilli, and are involved in the absorption of the cerebrospinal fluid (CSF). Defect in ependymal cells leads to hydrocephalus. As such, I sought to determine molecular mechanism underlying development of ependymal cells using a zebrafish model.
Methods: Spinal cords of zebrafish larvae were examined for the presence of ependymal cells by electron microscopy, and for a specific marker gene for ependymal cells by in situ RNA hybridization. Antisense oligonucleotide morpholino (MO) against cx43 was injected into zebrafish embryos to determine a loss-of-function phenotype of cx43, and Sonic hedgehog (Shh)

mutant embryos were subjected to in situ hybridization with cx43 riboprobes to check if Shh signaling is involved in the development of ependymal cells. In addition, in situ hybridization with cx43 riboprobes was performed on larvae treated with cyclopamine, a Shh signaling inhibitor, to confirm the finding obtained from Shh mutant larvae. Finally, Quantum dot was injected into the ventricle of larvae and the diffusion rate of the Quantum dot into the central canal was assessed.
Results: In situ hybridization with cx43 riboprobes revealed that cx43 was specifically expressed in the ependymal cells in the developing spinal cord. In addition, ependymal cells in the human spinal cord were shown to specifically express Cx43, as demonstrated by immunohistochemistry with anti-connexin43 antibody and anti-acetylated tubulin antibody. Cx43 morphants showed defect in ependymal cell development, which was rescued by microinjection of mouse cx43 RNA. Defect in ependymal cell development was observed in Shh mutant embryos and cyclopamine-treated embryos. cx43 morphants exhibited slower rate of diffusion of Quantum dot, which was injected into the ventricle of larvae, into the central canal than did control larvae.
Conclusion: cx43 is a marker gene for ependymal cells both in zebrafish and human, and plays an important role in ependymal cell development. Furthermore, Shh signaling is involved in the ependymal cell development.

Disclosures: J. Kim: None. **I. Jung:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant AG048284
NRF Grant 2017R1A5A2015391
NRF Grant 2016R1C1B2008772

Title: Fubp1 controls neural stem cell differentiation through cooperation with notch

Authors: *D.-Y. KIM[1], M. KANG[1], I. HWANG[2], T.-J. KIM[1], J. SUNG[1], J. PAIK[2]
[1]Dept of Pharmacology, Sch. of Dent., Kyungpook Natl. Univ., Daegu, Korea, Republic of;
[2]Dept. of Pathology and Lab. Med., Weill Cornell Med., New York, NY

Abstract: Neural stem cells (NSCs) are pluripotent self-renewing cells, which can give rise to new neurons and glial cells. As candidates of cell therapy for central nervous system injury or degenerative diseases, massive progress toward understanding NSCs has been made in recent decades. However, stem cell-based therapies still showed several problems such that the grafted NSCs maintain the undifferentiated states and fail to differentiate into appropriate neurons, or

that the grafted cells are developed into tumor cells. Therefore, characterization of NSCs fate decision mechanisms and identification of key factors regulating NSCs differentiation should be critical pre-requisites for NSC-based therapies. Here, we demonstrate that Fubp1 is highly expressed in proliferating neural stem/precursor cells (NSPCs) and Fubp1 expression is gradually reduced in the early phase of NSPC differentiation. We also showed that modulation of Fubp1 level influences NSPC fate regulation. We propose that functional interaction between Fubp1 and Notch pathway contributes to the maintenance of NSPC homeostasis.

Disclosures: D. Kim: None. **M. Kang:** None. **I. Hwang:** None. **T. Kim:** None. **J. Sung:** None. **J. Paik:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.11/A11

Topic: A.01. Neurogenesis and Gliogenesis

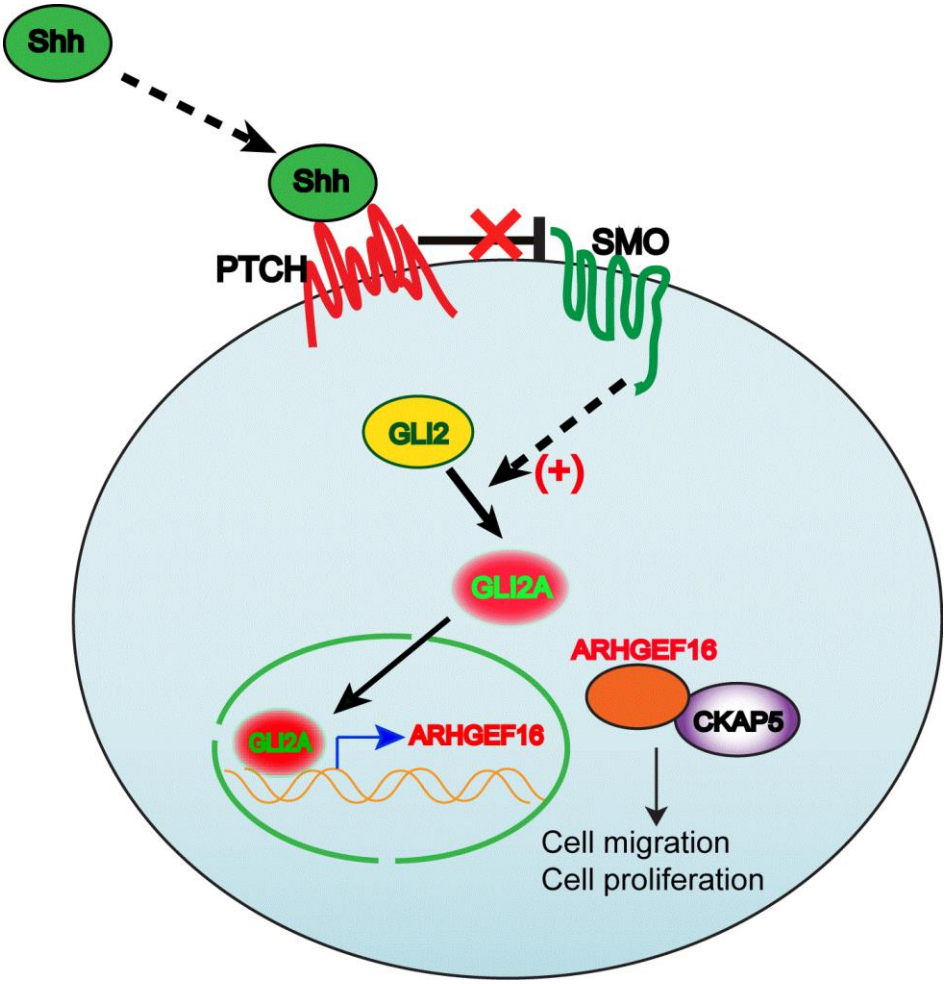
Support: National Natural Science Foundation of China 31460305
National Natural Science Foundation of China 31671476
Natural Science Foundation of Jiangxi Province 20171ACB20028

Title: GLI2 promotes cell proliferation and migration through transcriptional activation of ARHGEF16 in human glioma cells

Authors: *L. CHEN[1], L. XU[2], D. HUANG[2], Y. WANG[2], M. CHENG[2], W. SHI[2], H. XIONG[2], D. ZALLI[3], S. LUO[2]
[1]Nanchang Univ., Jiangxi, China; [2]Nanchang Univ., Nanchang, China; [3]Queen Mary Univ. of London, London, United Kingdom

Abstract: The Hedgehog (Hh) signaling pathway plays critical roles in modulating embryogenesis and maintaining tissue homeostasis, with glioma-associated oncogene (GLI) transcription factors being the main mediators. Aberrant activation of this pathway is associated with various human malignancies including glioblastoma, although the mechanistic details are not well understood. We addressed this question in the present study by performing a microarray analysis of genes that are differentially expressed in glioblastoma U87 cells overexpressing GLI2Arelative to the control cells. We found that *Rho guanine nucleotide exchange factor* (*ARHGEF*)*16* mRNA level was upregulated in U87 cells overexpressing GLI2A—the active form of GLI2—relative to control cells. The results of chromatin immunoprecipitation and dual-luciferase assays revealed that GLI2 binds to the *ARHGEF16* promoter and activates gene transcription. U87 and U118 cells overexpressing ARHGEF16 showed enhanced migration and proliferation relative to control cells, as determined by transwell migration and soft-agar colony

formation assays, respectively. A yeast two-hybrid assay revealed that ARHGEF16 interacts with cytoskeleton-associated protein (CKAP)5 and that this association is important for the stimulatory effects of ARHGEF16 on glioma cell migration and proliferation. These results suggest that therapeutic strategies
targeting the GLI2/ARHGEF16/CKAP5 signaling axis could inhibit glioma progression and recurrence.



Disclosures: L. Chen: None. **L. Xu:** None. **D. Huang:** None. **Y. Wang:** None. **M. Cheng:** None. **W. Shi:** None. **H. Xiong:** None. **D. Zalli:** None. **S. Luo:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH RO1 EY07060

Title: The small regulatory cytokine, Midkine-a, mediates stem cell proliferation and microglial phagocytosis during photoreceptor regeneration in zebrafish

Authors: *M. NAGASHIMA, P. F. HITCHCOCK
Univ. of Michigan, Ann Arbor, MI

Abstract: Midkine (Mdk) is a small, heparine-binding cytokine/growth factor that has multiple roles in neural development, repair and disease. During retinal development in zebrafish, *midkine-a*/Mdka, one of two paralogous *midkine* genes, functions to govern elements of the cell cycle. To explore the role of Mdka during regenerative neurogenesis, we generated mutant zebrafish using CRISPR-Cas9 gene editing and compared the death and regeneration of photoreceptors in wildtype and mutant animals. In Mdka mutants, the intrinsic retinal stem cells respond to the selective death of photoreceptors by dedifferentiating, characterized by increased expression of stem cell-associated genes, such as Rx1 and Sox2, however, reentry cell into the cell cycle is significantly diminished, resulting in reduced number of regenerated photoreceptors. This result indicates that Mdka is required for the intrinsic stem cells to enter the cell cycle, a result that is consistent with the role of Mdka in governing cell cycle kinetics during retinal development. In addition, in Mdka mutants, microglia respond abnormally to the apoptotic death of photoreceptors. Although the photoreceptor death follows a time frame observed for wildtype animals, microglia fail to phagocytose the dying photoreceptors, resulting in the persistence of apoptotic nuclei and the accumulation of reactive microglia in the photoreceptor layer. These results suggest that Mdka also plays a role in orchestrating inflammatory events following neuronal death and mediates the interaction between microglia and dying photoreceptors.

Disclosures: M. Nagashima: None. **P.F. Hitchcock:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.13/A13

Topic: A.01. Neurogenesis and Gliogenesis

Support: California Institute for Regenerative Medicine (CIRM) pre-doctoral fellowship
Hillblom Predoctoral Fellowship
NIH Ruth L.Kirshtein National Service Award (F31-AG050415)
NIA (R01-AG053382)
Glenn Foundation

Title: Classical MHC I molecule, H2-K^b, negatively regulates neural stem cell function through inhibition of FGFR1 signaling

Authors: *K. LIN[1], S. MÜLLER[2], L. K. SMITH[1], S. A. VILLEDA[1]
[1]Anat., [2]Neurosurg., UCSF, San Francisco, CA

Abstract: Proteins of the major histocompatibility complex class I (MHC I), previously known mainly for antigen presentation in the immune system, have recently been shown to be necessary for both developmental neural refinement and adult synaptic plasticity. However, their roles in non-neuronal cell populations in the brain have yet to be investigated. Our study identifies classical MHC I molecule H2-K^b as a negative regulator of proliferation in neural stem cells (NSCs), a cell type conferring inherent regenerative capacity to the brain. Adult animals with a genetic deletion ($K^{-/-}$) or acute knockdown of H2-K^b in the dentate gyrus exhibit enhanced cell division and an increased number of adult-born neurons in the hippocampus. This proliferative phenotype is recapitulated in cultured $K^{-/-}$ NSCs devoid of influences from the neurogenic niche or systemic environment, suggesting the effects are cell type specific. Subsequent transcriptomic analysis of $K^{-/-}$ and wild type NSCs further revealed that endogenous H2-K^b molecules inhibit NSC proliferation by dampening growth factor receptor signaling pathways, through a physical interaction with fibroblast growth factor receptor 1. These findings identify H2-K^b as a potential therapeutic target in neurodegenerative disorders or aging, where neurogenic dysfunction is a hallmark.

Disclosures: K. Lin: None. **S. Müller:** None. **L.K. Smith:** None. **S.A. Villeda:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.14/A14

Topic: A.01. Neurogenesis and Gliogenesis

Support: Catedra CONACYT 1840

Title: Systemic effect of a neurogenesis marker in a murine model

Authors: A. A. BARRIENTOS-BONILLA[1], P. B. PENSADO-GUEVARA[1], A. PUGA-OLGUIN[2], L. M. ZAVALA-FLORES[3], A. VILLANUEVA-OLIVO[4], I. T. CIBRIAN-LLANDERAL[5], *D. HERNANDEZ-BALTAZAR[6]
[1]Facultad de Química Farmacéutica Biológica, [2]Inst. de Neuroetología, Univ. Veracruzana, Xalapa, Veracruz, Mexico; [3]Ctr. de Investigación Biomédica del Noreste, Monterrey, Nuevo León, Mexico; [4]Facultad de Medicina, Univ. Autónoma de Nuevo León, Monterrey, Nuevo

León, Mexico; [5]Univ. Veracruzana, CONACYT-Instituto de Neuroetologia, Mexico, Mexico; [6]Inst. de Neuroetologia, CONACYT-Instituto de Neuroetologia., Mexico, Mexico

Abstract: Introduction. 5 Bromo 2 Deoxyuridine (BrdU) is a marker of neurogenesis widely used in animal models[1]. To date, it is unknown if the systemic administration of BrdU has a cytotoxic effect. In this study, we evaluated the physiological impact that multiple intraperitoneal administrations of BrdU, over 384 h, has in the liver of male and female Wistar rats. **Methodology.** This study was carried out with 21 rats divided in groups by sex and into subgroups (n=3). The male rats were distributed into the subgroups: 1) Control (intact), 2) 30% hepatectomy (HP) without receiving administration of BrdU (HP - BrdU), 3) HP + BrdU, and 4) incision at muscular level (Sham). The female rats were distributed into the subgroups: 1) Control (intact), 2) HP + BrdU and 3) Ovariectomized (24 h previous) + HP + BrdU. BrdU (50 mg/kg) was administered intraperitoneally. The volume corresponding to the weight of each rat was prepared in 250 μL of 0.1 M PBS, starting from a stock diluted in 50 μL of DMSO. The administrations of BrdU were applied at 12, 24, 48, 96, 144, 192 and 384 h post HP. Sham subgroup was euthanized the same day. The rest of the subgroups were euthanized at 384 h. **Results**. There was a survival rate of 96.7% and the animals showed dynamism similar to control groups. Liver function was assessed at a biochemical level. Total protein content, albumin, AST and LDH showed no significant difference in regard to the controls, between treatments (or sexes).As for total and conjugated bilirubin, only the group of male rats that did not receive BrdU showed significant increase (5.07x and 6.19x vs control respectively). The alkaline phosphatase content showed no significant difference between the BrdU group and the controls. The incorporation of rats with previous ovariectomy did not evidence significant differences with their control. However, the administration of BrdU induced the increase of 1.68x the levels of ALT in regard to control in male rats. **Discussion**. HP induces alteration in bilirubin and alkaline phosphatase levels demonstrated in the hepatic regenerative process. Ovariectomy does not affect the levels of analytes studied, which implies a component of susceptibility due to sex. An incision at muscular level induces an increase in ALT levels. Therefore, the observed increase in ALT levels in the BrdU group is due to the surgery and the mechanical stimulation due to injection[2,3]. **Conclusion.** Repeated administrations of BrdU (50 mg/kg) over 384 h in male and female Wistar rats did not induce significant alteration in the liver function tests. References
1. Kuhn and Kuhn. 2011. Curr Pharm Biotechnol. 2007.
2. Aller et al. World J Hepatol. 2012.
3. Webster AF, Williams A, Recio L, Yauk CL. Toxicol. 2014.

Disclosures: A.A. Barrientos-Bonilla: None. **P.B. Pensado-Guevara:** None. **A. Puga-Olguin:** None. **L.M. Zavala-Flores:** None. **A. Villanueva-Olivo:** None. **I.T. Cibrian-Llanderal:** None. **D. Hernandez-Baltazar:** None.

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636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.15/A15

Topic: A.01. Neurogenesis and Gliogenesis

Support: Department of Defense (CDMRP Award W81XWH-14-1-0572 to AKS)
Department of Veterans Affairs (VA Merit Award, I01BX002351 to AKS)

Title: MicroRNA expression in brain exosomes is altered in a Kainate model of chronic Temporal Lobe Epilepsy

Authors: *D. GITAI[1,2], Y. DOS SANTOS[1], R. UPADHYA[2,3], M. KODALI[2,3], A. K. SHETTY[2,3]
[1]Federal Univ. of Alagoas, Maceio, Brazil; [2]Inst. For Regen Med, Texas A&M Univ. Coll Med., College Station, TX; [3]Res. Service, Olin E. Teague Veterans' Med. Ctr., Temple, TX

Abstract: Temporal lobe epilepsy (TLE), the most common type of epilepsy, is often medically intractable. An initial precipitating injury to the brain resulting from a variety of causes underlies TLE in most cases, as such injury leads to the development of multiple epileptogenic changes in the hippocampus and the establishment of chronic epilepsy typified by spontaneous seizures. Precise mechanisms underlying the transformation of the injured hippocampus into an epileptic hippocampus are still unclear. We hypothesize that brain exosomes released from neurons and glia play an important role in epileptogenesis and the maintenance of chronic epilepsy. This premise is based on the ability of exosomes to facilitate the cross-talk between different types of neurons and neurons and glia through the release of their cargo (miRNAs, proteins, and lipids). These interactions can modulate function through activation or repression of multiple pathways. In this study, we compared the miRNA profile of brain exosomes in naïve and chronic epilepsy conditions using a Kainate-model of TLE. Brain exosomes were isolated by ultracentrifugation, characterized using Nanosight, electron microscopy and western blotting for CD63, and then processed for RNA-Seq. The exosomes from chronically epileptic brains displayed downregulation of 3 miRNAs (miR-187-5p, miR-346 and miR-331-3p) and upregulation of 4 miRNAs (miR-490-5p, miR-376b-3p, miR-493-5p and miR-124-5p) with fold changes ranging from 1.5 to 2.4 ($p<0.0006$; FDR<0.05). Bioinformatic analyses using microT-CDS and TargetScan tools retrieved a list of predicted target genes. Pathway analysis was performed by KEEG database to determine the biological significance of these targets and evaluate their representation. For some miRNAs, we observed overrepresentation of signaling pathways that are linked to molecular mechanisms underlying spontaneous seizures and chronic epilepsy, such as GABA-ergic synapses (miR-346 targets), spliceosomes (miR-331-3p targets) and gap junctions (miR-493-5p targets). Validation of the differential expression of identified miRNAs

and their targets in the epileptic brain through RT-qPCR and western blotting assays are underway. The results suggest that certain miRNAs in brain exosomes participate in maintaining a chronic epileptic state, which may be important for understanding the pathophysiology of TLE as well as developing promising therapeutic targets.

Disclosures: D. Gitai: None. **Y. dos Santos:** None. **R. Upadhya:** None. **M. Kodali:** None. **A.K. Shetty:** None.

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636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.16/A16

Topic: A.01. Neurogenesis and Gliogenesis

Support: State of Texas

Title: Intranasal administration of exosomes from human iPSC-derived NSCs enhances neural stem/progenitor cell proliferation and neurogenesis in the normal adult hippocampus

Authors: *A. K. SHETTY[1,2], R. UPADHYA[1], S. ATTALURI[1], M. PINSON[1], J. XU[1], B. SHUAI[1]
[1]Dept. of Mol. and Cell. Med., Inst. For Regen Med, Texas A&M Univ. Coll Med., College Station, TX; [2]Res. Service, Olin E. Teague Veterans' Med. Center, CTVHCS, Temple, TX

Abstract: Exosomes are tiny extracellular vesicles secreted by cells. They carry a cargo of miRNAs, proteins, and lipids and are involved in cell-cell communication as well as transmission of disease. Conversely, exosomes derived from stem cells such as mesenchymal stem cells and neural stem cells (NSCs) have neuroprotective and antiinflammatory properties. Such exosomes may also have neurogenic properties. The use of stem cell-derived exosomes for enhancing brain function in normal and disease conditions is attractive as they can be harvested, characterized and banked for prolonged periods. Their small size makes them particularly amenable for administration to the brain via relatively non-invasive intranasal (IN) and intravenous routes. The use of EVs also avoids several potential safety hazards linked with cells such as the risk for tumors. Our previous study has shown that IN administered exosomes can enter virtually all regions of the forebrain and get incorporated into neurons and microglia (Castro et al., SFN abstracts, 2017). Here, we examined the neurogenic property of exosomes generated from human induced pluripotent stem cell (hiPSC)-derived NSCs. We generated NSCs from hiPSCs using standardized methods and then expanded NSCs in adherent cultures. The conditioned media containing NSC-derived exosomes was next processed for a concentration step followed by ion exchange chromatography (Kim et al., PNAS, 2016). The exosomes were further concentrated using 100kDa ultrafiltration columns. Nanosight analysis revealed that the

size of exosomes varied from 50-120 nm (average size, 103 nm). hNSC-derived exosomes also expressed the exosome marker CD63. We administered these exosomes intranasally to mildly-anesthetized adult (6 months old) male rats (~62.5 billion exosomes/nostril, ~125 billion/rat) and examined NSC behavior and neurogenesis in the subgranular zone (SGZ) of the hippocampus 14 days after administration. Measurement of Ki-67 expressing cells in the SGZ revealed the proliferation of increased numbers of putative NSCs in animals receiving IN exosomes, in comparison to animals receiving IN vehicle ($p<0.01$). Moreover, Ki-67+ cell clusters in the SGZ of exosome treated animals were larger, more frequent and comprised a higher number of cells per cluster ($p<0.01$). Doublecortin (DCX+) immunostaining also revealed increased numbers DCX+ clusters containing higher numbers of immature neuroblasts ($p<0.05$). Additional analyses of neurogenesis are underway. Thus, hiPSC-NSC derived exosomes have neurogenic properties. These exosomes may be suitable as biologics for enhancing hippocampal neurogenesis in conditions such as aging and disease.

Disclosures: A.K. Shetty: None. **R. Upadhya:** None. **S. Attaluri:** None. **M. Pinson:** None. **J. Xu:** None. **B. Shuai:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.17/A17

Topic: A.01. Neurogenesis and Gliogenesis

Support: CDMRP Award W81XWH-14-1-0572
VA Merit Award, I01BX002351

Title: Status epilepticus leads to increased concentration of neuron-derived exosomes in the blood with downregulation of mir-363-5p, mir-322-3p, and mir-320-3p

Authors: *M. LEELAVATHI NARAYANA[1], R. UPADHYA[1,2], S. ATTALURI[1], B. SHUAI[1,2], M. KODALI[1,2], D. GITAI[1], A. K. SHETTY[1,2]
[1]Inst. For Regen Med, Texas A&M Univ. Coll Med., College Station, TX; [2]Olin E. Teague Veterans' Med. Center, CTVHCS, Temple, TX

Abstract: Status epilepticus (SE) causes neurodegeneration and neuroinflammation in the brain when seizures are not extinguished quickly. An episode of SE may lead to temporal lobe epilepsy (TLE) typified by partial complex seizures and cognitive dysfunction. Yet, the progression of SE into TLE is difficult to envisage as it depends on the extent of the injury, neuroinflammation, and epileptogenic changes. Hence, finding blood biomarkers that predict whether a particular SE episode would result in TLE has importance. Exosomes released from neurons and glia into the bloodstream have promise as biomarkers of SE-induced TLE because

the composition of exosomes (microRNAs, lipids, and proteins) is likely altered after injury. As exosomes express specific markers, it is also possible to track them to the cell of origin. We developed methods to isolate neuron-derived exosomes (NDE) and astrocyte-derived exosomes (ADE) in the blood. We induced SE via Kainate injections, terminated seizures through a diazepam injection at 2h after SE onset, and collected blood at 24h after SE. We first segregated exosomes from the serum using ExoQuick kit (Systems Bio) and then separated NDE and ADE using biotinylated antibodies for CD171 (a marker of NDE) and glutamine aspartate transporter (a marker of ADE), and streptavidin-based resin. Analyses using Nanosight revealed a decreased number of total exosomes but increased numbers of NDE and ADE in the blood after SE ($p<0.05$). NDE and ADE were similar in size (64-83 nm) but were smaller than the average size of all blood exosomes (115-125 nm). All exosomes expressed the membrane marker CD63. miRNA-sequencing revealed that the top 10 abundant miRNAs in NDE and ADE were similar in both control and SE conditions. However, 4 miRNAs displayed differential expression between NDE and ADE in naïve animals. Importantly, 3 miRNAs (miR-363-5p, miR-322-3p, and miR-320-3p) in NDE were downregulated after SE. These miRNAs are involved in regulation of neurite outgrowth (miR-363-5p, Quan et al., Neurochem Res, 2017), neoangiogenesis (miR-322-3p, Altintas et al., Neurological Res, 2016), apoptosis, IGF-1 signaling, and depressive phenotype (miR-320-3p, Camkurt et al., J Psychiatr Res, 2015). Bioinformatic analyses to retrieve a list of predicted target genes is underway. Thus, isolation of NDE and ADE from the blood is feasible for biomarker discovery in neurodegenerative conditions through RNA-Seq studies. Increased NDE and ADE in the blood after SE is likely linked to neuronal hyperactivity and astrocyte reactivity. Downregulation of 3 specific miRNAs in NDEs after SE may be linked to epileptogenic processes that ensue after SE.

Disclosures: M. Leelavathi Narayana: None. **R. Upadhya:** None. **S. Attaluri:** None. **B. Shuai:** None. **M. Kodali:** None. **D. Gitai:** None. **A.K. Shetty:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.18/A18

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSFC Grant 81571615

Title: MHCI molecules regulate cell proliferation of central nervous system during embryonic period stage

Authors: *P. LI[1], Y. SHEN[2], Y. HU[1], J. ZHANG[2]
[1]Inst. Of Life Sciences, Southeast Univ., Jiangsu, China; [2]Med. School, Southeast Univ., Jiangsu, China

Abstract: Background: Classical major histocompatibility complex class I (MHCI), first identified in the immune system, are well known for their role in the vertebrate adaptive immune response. Recent studies have shown that major histocompatibility complex (MHCI) proteins are expressed in postnatal central nervous system (CNS) where they play important roles in neuron development and synaptic plasticity. We reported that MHCI protein was widely expressed by neural progenitors in the subventricular zone where neurogenesis take place. In addition, MHCI proteins were co-expressed with the nestin-positive cells in telencephalon during E10.5. However, the functions of MHCI molecules during the initial development of CNS still remain unknown. **Methods and results:** In the present study, we attempt to determine whether MHCI molecules have effects on neurogenesis in mouse CNS at embryonic stage using littermate wild type and H2-DbKb Knock out (KO) mice. Littermate mice were injected BrdU at E15.5 and E17.5, then brain tissue were collected 20 minutes later. Immunofluorescence staining showed cell numbers that positively stained with proliferation marker PH3, BrdU and Ki67-positive decreased in H2-DbKb KO mice, suggesting the proliferation of progenitor cells reduced in KO mice. Besides that, cell numbers of double immunostaining of GFP and the BrdU were found to be elevated by overexpression of H2-Db-GFP in wild type mice from E15.5 to E16.5 by in utero eletroporation. In contrast to that, when we knocked down non-classical MHCI molecules H2-M3 using GFP expression plasmid with shRNA targeting H2-M3, the number of double positive cell decreased. **Conclusions:** Although the development of H2-DbKb KO mice was reported to be normal, our results showed that both classical and non-classical MHCI molecules have an effect on neuronal proliferation in the embryonic period. As we reported before, the expression of non-classical MHCI molecules were increased in H2-DbKb KO mice, which might compensate for loss of classical MHCI molecules. Moreover, we are exploring the effect of MHCI molecules on neuronal migration and differentiation during embryonic development. In conclusion, this study will extend previous findings by suggesting a novel role on neuronal MHCI molecules during neurogenesis.

Disclosures: P. Li: None. **Y. Shen:** None. **Y. Hu:** None. **J. Zhang:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.19/A19

Topic: A.01. Neurogenesis and Gliogenesis

Support: NJCAUT #17BSP010

Title: Systemically elevating Interleukin-6 in neonatal male mice enhances the production of multipotential progenitors at the expense of neural stem cells

Authors: *S. W. LEVISON[1], E. KUMARI[1], A. NASUHIDEHNAVI[1], V. H. SAVANUR[1], K. D. BUONO[1,2]
[1]Pharmacology, Physiol. and Neurosci., Rutgers Univ., Newark, NJ; [2]ICON Lab. Services, Farmingdale, NY

Abstract: A number of studies have highlighted the connection between infections during pregnancy and increased risk for autism leading to the view that maternal immune activation (MIA) is a significant contributor to autism spectrum disorder (ASD) incidence. Cytokines produced maternally can cross the placenta to affect the developing brain. However, it is not clear how these cytokines alter the trajectory of neural development. In our studies on the effects of inflammation on the cells of the subventricular zone (SVZ), we have established that one of the key cytokines implicated in ASD, interleukin-6 (IL-6) directly affects the neural stem cells and progenitors that reside in this region. SVZ neural stem cells and progenitors express both the IL-6 receptor and GP130 and 30 minutes following addition of 5 ng/mL IL-6 to neurosphere cultures, STAT-3 phosphorylation increases 10-fold and STAT-1 phosphorylation increases 4-fold, but phosphorylated ERK and AKT are unchanged. When neurospheres are maintained in culture for 6 days in IL-6 supplemented medium, sphere self-renewal and tripotentiality are enhanced. However, this is due to an increase in the proportion of PDGF/FGF2 responsive multipotent progenitors (PFMPs) with a decrease in the proportion of neural stem cells; and can be attributed to increased PFMP proliferation. To studythe effects of systemically increased IL-6 on SVZ cells and brain development,40 ng IL-6 was injected i.p., which doubled the circulating concentration of IL-6, similar to that documented for ASD patients. When postnatal day 4 male Swiss Webster mice were administered 3 doses of IL-6 every 12 hours followed by a single injection of EdU, the proportion of EdU+ PFMPs (but not other progenitors) was increased 2-fold compared to PBS injected controls. Altogether, these studies show that IL-6 alters the proportion of multipotential progenitors and stem cells in the SVZ, which may have important consequences for brain development and function. Supported by grant #CAUT17BSP010 from the Governor's Council for Medical Research and Treatment of Autism awarded to SWL.

Disclosures: S.W. Levison: None. **E. Kumari:** None. **A. Nasuhidehnavi:** None. **V.H. Savanur:** None. **K.D. Buono:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.20/A20

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSFC(31200798,20131351353)
Tsinghua CLS funds

Title: Extracellular matrix-associated CYR61 maintains neural stem cells during forebrain development

Authors: *J. ZHENG[1,2,3], S. QI[1,2,3], J. WU[1,2,3], Q. SHEN[2,3]
[1]Dept. of Basic Med., Tsinghua Univ., Beijing City, China; [2]Col. of Life Sci. and Technol., Tongji Univ., Shanghai City, China; [3]Brain and Spinal Cord Innovative Res. Ctr., Tongji Hosp., Shanghai City, China

Abstract: Neural stem cells (NSCs) are capable of self-renewal and differentiation into multiple neural cell types. NSCs and their progeny reside in microenvironment called stem cell niches, which consist of extracellular matrix (ECM), soluble factors, and neighboring cell types are functional components of NSC niche. Here, we investigate the role of an extracellular matrix associated signaling protein, cysteine-rich angiogenic inducer 61 (*Cyr61*) during the development of NSCs in the forebrain. *Cyr61* belongs to the CCN family, also known as CCN1 or insulin-like growth factor binding protein 10 (IGFBP10). By *in situ* hybridization, we found that *Cyr61* specifically expressed in radial glial cells (RGCs) in the embryonic forebrain, enriched in the apical side along the ventricular surface. The expression of *Cyr61* becomes restricted to ependymal cells at postnatal stages. In a binding assay applying recombinant CYR61 human Fc (CYR61-huFc) protein to NSC culture or forebrain wholemount culture, we found that CYR61 only bound to Nestin+ radial glial cells but not Tuj1+ neurons both *in vitro* and *ex vivo*. Overexpression of *Cyr61* through *in utero* electroporation (IUE) at embryonic (E) 12.5 to E14.5 increased Sox2+ neural progenitors in the lateral ganglionic eminence (LGE). Moreover, prolonged overexpression of CYR61 in the dorsal cortex from E14.5 to postnatal day 7 maintained neural progenitors in cortical germinal zones. We found that overexpression of *Cyr61* by IUE in the dorsal cortex resulted in up-regulation of genes related to neural stem cell identity, including Pax6, Sox2, and VCAM1 by RNA-seq analysis of fluorescence-activated cell sorted (FACS) *Cyr61*-overexpressing cortical cells. Additionally, we demonstrated that IGF2 interacted with mouse CYR61 by co-immunoprecipitation in transfected 293FT cells. Ongoing studies are to identify CYR61-interacting proteins in the embryonic forebrain *in vivo* using pull down assay followed by mass spectrometry analysis. We are investigating the phenotypes of $Nestin^{cre}/Cyr61^{fl/fl}$ mice to characterize the role of *Cyr61* during early neural development. Our study will help us understand the role and working mechanisms of NSC niche factors such as *Cyr61* in NSC maintenance and differentiation.

Disclosures: J. Zheng: None. **S. Qi:** None. **J. Wu:** None. **Q. Shen:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.21/A21

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Natural Science Foundation of China (Grant: 31471042)

Title: Resolving cellular equipotency of developing optic vesicles

Authors: *B. XU, H. WANG, J. YAN, J. HE
Inst. of Neuroscience, CAS, Shanghai City, China

Abstract: In the CNS development, symmetric proliferation characterizes the initial stages, where individual progenitors produce two daughter progenitors. The assumption of cellular equipotency of these progenitors is fundamentally important, but has not been tested in-vivo. To test this, we analyzed progenitors of developing optic vesicles in zebrafish. Modeling of clonal dynamics revealed that PP progenitors exhibit the unified cell-cycle dynamics. Further clonal analysis at consecutive lineage stages and heterochronic transplantation showed that as lineage progresses, PP progenitors are equivalent in proliferative potentials, change in which counts on environmental cues but not cell division. Furthermore, stochastic absence of individual retinal fates from sister clones of PP progenitors suggested no fate restriction. Surprisingly, single-cell RNA-seq demonstrated that stochastic gene expression characterizes this cellular equipotency. This study provides the framework to assess cellular equipotency and demonstrates the stochastic mitosis of equipotent progenitors as the major cellular mechanism driving the early CNS development.

Disclosures: B. Xu: None. **H. Wang:** None. **J. Yan:** None. **J. He:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.22/A22

Topic: A.01. Neurogenesis and Gliogenesis

Support: UL1 TR001860 and linked award TL1 TR001861
Shriners Hospital Grant 86700-NCA
NIH Grant R01NS073055
NSF Grant 1120796
NIH Grant R01DE022830

Title: Mechanisms of selective autophagy-mediated regulation of neuronal differentiation during nervous system development

Authors: *A. LEE[1], K. ZARBALIS[2], L. N. BORODINSKY[1]
[1]Univ. of California Davis, Sacramento, CA; [2]Dept. Pathology/IPRM, UC Davis/Shriners Hosp. for Children, Sacramento, CA

Abstract: The autophagy factor Wdfy3 is critical for mouse and human brain development. In humans, *WDFY3* genetic mutations are associated with autism, macrocephaly, or familial microcephaly and intellectual disability. In mice, *Wdfy3* loss-of-function has been shown to alter the transition from neural stem cell to intermediate neuronal progenitor and to cause axonal outgrowth defects. However, the precise mechanisms by which Wdfy3 regulates these processes remain unclear.
Using *Xenopus laevis* and mouse, we aim to determine the mechanisms of Wdfy3-dependent regulation of neurogenesis and axonal outgrowth. We hypothesize that Wdfy3 regulates neural stem cell proliferation, neuronal differentiation and axonal outgrowth through autophagic removal of ubiquitinated proteins. Reverse transcriptase PCR indicates *wdfy3* is expressed during different stages of *Xenopus laevis* development. Fluorescent immunohistochemistry staining shows that Wdfy3 is present in the frog tadpole spinal cord, and brain. Wdfy3 protein appears enriched in neurons compared to neural stem cells, and is present in neurites.
To assess the function of Wdfy3 in *Xenopus laevis* nervous system development, we injected a Wdfy3 translation-blocking morpholino at 2-cell stage embryos and performed EdU cell proliferation assays followed by immunostaining for the neural stem cell marker Sox2. Results show that the number of Sox2-immmunopositive cells in the forebrain increases when Wdfy3 is knocked down, suggesting an increase in neural stem cell expansion in the affected brain. Moreover there are fewer Wdfy3-morpholino-containing cells with highest EdU-labeling compared with the wild type counterparts, suggesting a higher rate of cell division in Wdfy3-deficient neural cells.
Wdfy3's effect on *Xenopus laevis* axonal outgrowth was assessed by morpholino-induced knockdown. Wdfy3 deficiency decreases the axonal density in brain commissures and in the axial musculature.
Further understanding of autophagy's role during neural development could lead to new treatments for neurodevelopmental and neurodegenerative disorders.

Disclosures: A. Lee: None. **K. Zarbalis:** None. **L.N. Borodinsky:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.23/A23

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5R21NS091865

NIH Grant 5R01NS032457
NIH Grant R24HL123482
Allen Discovery Center program
Howard Hughes Medical Institute

Title: Aspm knockout ferret reveals an evolutionary mechanism governing cerebral cortical size

Authors: *B.-I. BAE[1], M. B. JOHNSON[2], A. KODANI[2], R. BORGES-MONROY[2], K. IM[3], J. F. ENGELHARDT[4], C. A. WALSH[2]
[1]Neurosurg., Yale Univ. Sch. of Med., New Haven, CT; [2]Genet. and Genomics, Boston Children's Hosp., Boston, MA; [3]Div. of Newborn Med., Children's Hosp. Boston, Boston, MA; [4]Univ. of Iowa, Iowa City, IA

Abstract: The human cerebral cortex is distinguished by its large size and abundant gyrification, or folding. However, the evolutionary mechanisms that drive cortical size and structure are unknown. Although genes that are essential for cortical developmental expansion have been identified from the genetics of human primary microcephaly (a disorder associated with reduced brain size and intellectual disability), studies of these genes in mice, which have a smooth cortex that is one thousand times smaller than the cortex of humans, have provided limited insight. Mutations in abnormal spindle-like microcephaly-associated (*ASPM*), the most common recessive microcephaly gene, reduce cortical volume by at least 50% in humans, but have little effect on the brains of mice; this probably reflects evolutionarily divergent functions of *ASPM*. Here we used genome editing to create a germline knockout of *Aspm* in the ferret (*Mustela putorius furo*), a species with a larger, gyrified cortex and greater neural progenitor cell diversity than mice, and closer protein sequence homology to the human ASPM protein. *Aspm* knockout ferrets exhibit severe microcephaly (25-40% decreases in brain weight), reflecting reduced cortical surface area without significant change in cortical thickness, as has been found in human patients, suggesting that loss of 'cortical units' has occurred. The cortex of fetal *Aspm* knockout ferrets displays a very large premature displacement of ventricular radial glial cells to the outer subventricular zone, where many resemble outer radial glia, a subtype of neural progenitor cells that are essentially absent in mice and have been implicated in cerebral cortical expansion in primates. These data suggest an evolutionary mechanism by which ASPM regulates cortical expansion by controlling the affinity of ventricular radial glial cells for the ventricular surface, thus modulating the ratio of ventricular radial glial cells, the most undifferentiated cell type, to outer radial glia, a more differentiated progenitor.

Disclosures: B. Bae: None. **M.B. Johnson:** None. **A. Kodani:** None. **R. Borges-Monroy:** None. **K. Im:** None. **J.F. Engelhardt:** None. **C.A. Walsh:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.24/A24

Topic: A.01. Neurogenesis and Gliogenesis

Support: CRC 1080
DFG 1193
China Scholarship Council

Title: Role of Hippo signalling in adult neural stem cell homeostasis

Authors: *W. FAN[1], J. JURADO ARJONA[1], S. PÉRON[1], C. BERGER[2], B. BERNINGER[1]
[1]Univ. Med. Ctr., Johannes Gutenberg Univ. Mainz, Mainz, Germany; [2]Inst. of Genet., Johannes Gutenberg Univ., Mainz, Germany

Abstract: Adult neural stem cells (aNSCs) residing in the subgranular zone (SGZ) of the dentate gyrus (DG) are finely regulated to precisely control the adult generation of newborn neurons. Quiescence is essential for long-term maintenance of aNSCs. Intrinsic factors, as well as extrinsic niche signals, orchestrate the balance between activation and quiescence of aNSCs but the mechanisms are still not completely understood.
Here we show that changes in Hippo signaling pathway affects the quiescence and activation of aNSCs in mice. We found that Yap1, one of the most important effector components in Hippo pathway, is specifically expressed in mouse aNSCs and astrocytes in SGZ, but not in other cell types such as neurons and oligodendrocytes. Moreover, levels of nuclear Yap1 significantly decrease in induced quiescent aNSCs. In vitro, overexpression of constitutively active Yap1 (5SA) induces the transition from quiescence to activated state of aNSCs. This effect is exerted through TEAD interaction, thereby, constitutively active version of Yap1 with a mutation in TEAD binding site (5SA/S94A) fails to activate quiescent aNSCs. In addition, pharmacological disruption of YAP1-TEAD complex decreases proliferation of aNSCs. These results indicate that Yap1-TEAD interaction is very important for aNSCs activation and proliferation. In vivo, overexpression of constitutively active Yap1 driven by hGFAP promoter, increases proliferation of aNSCs dramatically at 7 dpi in DG. Moreover, overexpression of Yap1 can also block differentiation of aNSCs and maintain them at progenitor stage (Sox2 positive) at 30 dpi. Collectively, we uncover a new mechanism which can regulate aNSCs development and exhibit the key role of Hippo signaling in aNSCs homeostasis.

Disclosures: W. Fan: None. **J. Jurado Arjona:** None. **S. Péron:** None. **C. Berger:** None. **B. Berninger:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.25/A25

Topic: A.01. Neurogenesis and Gliogenesis

Support: UCSF Program for Breakthroughs in Biomedical Research, Sandler Foundation
UCSF Resource Allocation Program Pilot Grant for Junior Investigators

Title: Dissecting the roles of store-operated calcium entry during development of the cerebral cortex

Authors: *A. ARJUN[1,2,3], S. LAUNER[2], J. TONG[2], R. I. PETROVA[1,2], Y. KHAN[2], G. PANAGIOTAKOS[1,2,3,4]
[1]Univ. of California San Francisco, San Francisco, CA; [2]Eli and Edythe Broad Ctr. of Regeneration Med. and Stem Cell Res., [3]Developmental and Stem Cell Biol. Grad. Program, [4]Kavli Inst. for Fundamental Neurosci., Univ. of California, San Francisco, San Francisco, CA

Abstract: Calcium signaling has been reproducibly implicated in a variety of developmental processes in the embryonic brain, including neural induction, neural progenitor cell (NPC) proliferation, neuroblast migration and differentiation. Mutations in genes encoding calcium signaling proteins have also been associated with neurodevelopmental disorders like autism spectrum disorders and intellectual disability, further highlighting key roles for calcium signaling during the development of the cerebral cortex. In the embryonic rodent cortex, agonist-induced calcium waves, mediated by the release of intracellular calcium stores, propagate through the germinal zones and modulate aspects of NPC proliferation. It is unclear, however, how internal calcium stores are regulated in cortical NPCs and how they are linked to the regulation of NPC function. Store operated calcium entry (SOCE), a mode of calcium influx tied to depletion of intracellular ER calcium stores, has been shown to regulate calcium influx and proliferation of NPCs *in vitro*, but its role in the embryonic cortex remains unexplored. Here, utilizing a combination of pharmacology and *in utero* gain- and loss-of-function approaches, we interrogate specific roles for SOCE in the embryonic cortex. We have found that functionally distinct isoforms of the STIM family of endoplasmic reticulum (ER) calcium sensors are dynamically regulated during neuronal differentiation, such that an inhibitory isoform of Stim2 is upregulated in young neurons. This observation is in line with previous work demonstrating that robust SOCE responses in NPCs *in vitro* are abolished upon differentiation into neuroblasts. We have also found that manipulating the levels of Stim2 variants using *in utero* electroporation at embryonic day 13 (E13) bidirectionally regulates cell cycle exit in dividing cortical NPCs. We are further exploring this observation using live imaging approaches, single cell RNA sequencing, and a variety of molecular and biochemical assays. Collectively, our data sheds light

on roles for the molecular mediators of SOCE in the regulation of proliferation and differentiation in the developing cortex.

Disclosures: A. Arjun: None. **S. Launer:** None. **J. Tong:** None. **R.I. Petrova:** None. **Y. Khan:** None. **G. Panagiotakos:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.26/A26

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSFC Grant 31200798
NSFC Grant 20131351353

Title: The long noncoding RNA lncNSPC is required for the maintenance of neural stem and progenitor cell (NSPC) potential

Authors: *S. QI[1,2,3], J. ZHENG[1,2,3], Q. BAI[2,3], Q. SHEN[2,3]
[1]Med. Sch., Tsinghua Univerity, Beijing City, China; [2]Tongji Univ., Shanghai, China; [3]Tongji Hosp., Shanghai, China

Abstract: Neocortical development involves cell proliferation, differentiation, migration and synaptic connection. This complex yet highly organized process is regulated by multi-layered mechanisms including transcriptional, epigenetic and environmental controls. Among various regulatory factors, long non-coding RNAs (lncRNAs) emerge as important epigenetic players during cortical development. Numerous lncRNAs have been identified in the developing brain. However, functions of these transcripts remain unexplored or elusive, especially at the early stage of neurogenesis. To identify lncRNAs that are differentially expressed in embryonic cortical neural stem and progenitor cells (NSPCs) versus in differentiating neurons, we performed a transcriptome analysis of early NSPCs and differentiating neurons by RNA-seq. We found that a poorly characterized lncRNA, which we called *lncNSPC* is specifically expressed in NSPCs in the embryonic cerebral cortex. In situ hybridization (ISH) on brain sections from E11 to E16 mouse embryos verified that *lncNSPC* is enriched in the germinal zone of the developing forebrain. Using subcellular fractionation and fluorescence in situ hybridization (FISH) assays, we revealed that *lncNSPC* is present in the cytoplasma of Neuro2a (N2a) cell lines or primary NSPCs. To investigate the roles of *lncNSPC* in NSPCs, we electroporated shlncNSPC or shluciferase (control) construct into neural stem cells in the embryonic cerebral cortex at E14.5. Two days later, we found that depletion of *lncNSPC* promotes cell cycle exit of NSPCs, accompanied by decreased TBR2 positive progenitor cells as well as increased neuronal differentiation when we co-electroporated a NeuroD1-GFP vector. Notably, we discovered that

partial deletion of the promoter and exon1 regions in *lncNSPC* locus by CRISPR/Cas9 does not affect the RNA levels of its neighboring coding genes in N2a cell lines. Using RNA pulldown assay, we identified potential binding partners of *lncNSPC* including RNA binding proteins. Therefore, *lncNSPC* , as a lncRNA, may participate in the regulation of neurogenesis through multiple mechanisms. We are further evaluating the target genes affected by *lncNSPC* and its binding partners in order to elucidate mechanisms of altered NSPC potential by reduced *lncNSPC*. This work will provide insights in regulatory roles of lncRNAs in the context of neural differentiation.

Disclosures: S. Qi: None. **J. Zheng:** None. **Q. Bai:** None. **Q. Shen:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.27/A27

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSFC 91232301
NSFC 31471041

Title: PDK1 regulates the transition of APs to BPs during the cortical neurogenesis

Authors: *Y. WEI[1], X. HAN[2], C. ZHAO[2], J. GAO[3]
[1]Inst. of Life Science,Southeast Univ., Jiangsu, China; [2]Southeast Univ., Jiangsu, China; [3]Nanjing Med. Univ., Jiangsu, China

Abstract: Abstract The mammalian neocortex consists of hundreds of neuron subtypes arising from two specific classes of neural stem cells (apical progenitors, Aps) and fate-restricted basal progenitor cells (BPs) during embryonic development. APs dividing at the ventricular zone (VZ) mainly give rise to deeper cortical neurons and BPs, while BPs undergoing mitosis at the subventricular zone(SVZ) mainly produce upper layer neurons. The timing of the transition from APs to BPs is critical for corticogenesis. However, the regulation of the transition is poorly understood. In this study, we first identified a peak expression level of the phosphoinositide-dependent protein kinase 1 (PDK1) during the period of E14.5-16.5, the time window when superficial neurons produced, suggesting a possible role for PDK1 regulating the balance between deeper and superficial neurogenesis. By crossing $PDK1^{fl/fl}$ mice with *Emx1*-Cre line, PDK1 was conditionally ablated in the dorsal cortex. We have found the overall neural output as well as the number of deeper neurons was increased with no obvious changes on superficial neurons at P0. Further studies show the transition from Aps to BPs is severely delayed after PDK1 deletion, and results in overproduction of deeper neurons. We have found the length of the G1 phase of AP cell cycle is shortened from E14.5 onwards and accompanied with impaired

interkinetic nuclear migration at ventricular zone. The division planes of PDK1-deficient APs are significantly more vertical than that of controls. In cell culture, NPCs display the tendency to take proliferative division instead of neurogenic division after PDK1 deletion, consistent with that observed in vivo. We have also demonstrated that by inhibiting activated atypical PKC (aPKC), the PDK1-aPKC pathway coordinating with Notch signaling to regulate the transition of Aps to Bps. Our findings provide new sight into cortical neurogenesis.

Disclosures: Y. Wei: None. **X. Han:** None. **C. Zhao:** None. **J. Gao:** None.

Poster

636. Neural Cell Proliferation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 636.28/A28

Topic: A.01. Neurogenesis and Gliogenesis

Support: NS041021

Title: The transcriptional regulator snon promotes the proliferation of granule neuron precursors in the brain in a temporally specific manner

Authors: *X. CHEN[1], D. WU[3], Y. IKEUCHI[4], J. GOODMAN[3], N. REDDY[3], S. MAJIDI[3], S. SMITH[3], A. GODEC[3], A. OLDENBORG[3], S. BONNI[5], H. GABEL[2], A. BONNI[6]
[1]Neurosci., [2]Anat. & Neurobio., Washington Univ. Sch. of Med., Saint Louis, MO; [3]Washington Univ. in St. Louis, St. Louis, MO; [4]Inst. of Industrial Sci., Tokyo, MO; [5]Dept. of Biochem. and Mol. Biol., Calgary, AB, Canada; [6]Dept. of Neurosci., Washington Univ. in St. Louis, Sch. of Medi, Saint Louis, MO

Abstract: ABSTRACT
Control of neuronal precursor cell proliferation is essential for normal brain development, and deregulation of this fundamental developmental event contributes to brain diseases. Typically, neuronal precursor cell proliferation extends over long periods of time during brain development. However, how neuronal precursor proliferation is regulated in a temporally specific manner remains to be elucidated. Here, we report that conditional knockout of the transcriptional regulator SnoN in granule neuron precursors in the mouse cerebellum robustly inhibits the proliferation of these cells and promotes their cell cycle exit specifically at later stages of cerebellar development in the postnatal brain. In gene profiling studies, SnoN regulates the expression of a program of cell proliferation genes in granule neuron precursors, whose pattern of expression and gene promoter-associated histone marks correlate temporally with SnoN-regulation of granule neuron precursor cell proliferation. In behavior analyses, conditional knockout of SnoN impairs cerebellar-dependent learning in a delayed eye-blink conditioning paradigm, suggesting that SnoN-regulation of granule neuron precursor proliferation bears

functional consequences at the organismal level. Our findings define a novel function for the major transcriptional regulator SnoN in the temporal control of granule neuron precursor proliferation in the mammalian brain.

Disclosures: X. Chen: None. **D. Wu:** None. **Y. Ikeuchi:** None. **J. Goodman:** None. **N. Reddy:** None. **S. Majidi:** None. **S. Smith:** None. **A. Godec:** None. **A. Oldenborg:** None. **S. Bonni:** None. **H. Gabel:** None. **A. Bonni:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.01/A29

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF Grant 1557414

Title: A novel mechanism for ephrin reverse signaling in the control of neuronal migration

Authors: *P. F. COPENHAVER, C. BATES, A. D. RAINHA, C. KAWAMOTO, H.-J. LEE
Cell & Developmental Biol., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Bidirectional signaling by Ephrins and Eph receptors can regulate many aspects of cell migration in the developing nervous system, but the mechanisms controlling these responses are only partially understood. Ephrin ligands stimulate conventional “forward” signaling by activating Eph receptors, but Eph receptors also induce “reverse” signaling via their cognate Ephrins. Investigating the mechanisms underlying these responses in vertebrates has been complicated by evidence that neurons often co-express multiple Ephrins and Eph receptors that can interact promiscuously. In contrast, the hawkmoth Manduca sexta expresses only one type-A Ephrin (GPI-linked MsEphrin) and one corresponding Eph receptor (MsEph). In previous work, we showed that reverse signaling via MsEphrin plays an essential role in regulating neuronal migration within the embryonic enteric nervous system (ENS). During ENS development, a population of ~300 neurons (EP cells) migrate along pre-formed visceral muscle bands while avoiding adjacent midline regions. The migratory neurons express GPI-linked MsEphrin, while MsEph receptors are confined to the midline muscle cells. Manipulations in embryo culture demonstrated that blocking endogenous MsEphrin-MsEph interactions resulted in ectopic midline crossing by the neurons, whereas forward signaling (via MsEph receptors) played no role in this process. We also showed that MsEphrin reverse signaling was transduced by a specific Src family kinase (Src42A): activating MsEphrin signaling significantly increased Src42A activity in the EP cells and inhibited their motility, whereas inhibiting Src42A activity precluded reverse signaling and caused midline crossovers (similar to blocking MsEphrin-MsEph interactions). We also showed that activation of Src42A induced RhoA-dependent

retraction responses away from the midline, defining the effector pathway underlying this response. In a screen for MsEphrin-interacting proteins that might directly activate Src42 during reverse signaling, we recently identified RACK1 (Receptor of Activated Protein Kinase C), a reciprocal regulator of Src family kinase (SFK) activity. We now have found that MsEphrin requires RACK1 to activate Src42, while Src42 is required for the inactivation of RACK1 during MsEphrin signaling. These results support the model that a "Src-RACK rheostat" plays a central role in the transduction of Ephrin-A reverse signaling. We are currently testing candidate co-receptors that may couple MsEphrin to the RACK1-Src42 complex, with the goal of understanding how Ephrin-A reverse signaling regulates neuronal migration during embryonic development.

Disclosures: P.F. Copenhaver: None. **C. Bates:** None. **A.D. Rainha:** None. **C. Kawamoto:** None. **H. Lee:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.02/A30

Topic: A.01. Neurogenesis and Gliogenesis

Support: OEAW DOC Fellowship
FP7 MC-CIG MomeCode 618444

Title: Cell-autonomous and non-autonomous mechanisms controlling projection neuron migration

Authors: *A. H. HANSEN[1], J. RENNO[1], C. STREICHER[1], S. LAUKOTER[1], F. M. PAULER[1], L. ANDERSEN[2], T. RUELICKE[2], S. HIPPENMEYER[1]
[1]IST Austria, Klosterneuburg, Austria; [2]Inst. of Lab. Animal Science, Univ. of Vet. Med., Vienna, Austria

Abstract: Concerted radial migration of newly born cortical projection neurons, from their birthplace to their final target lamina, is a key step in the assembly of the cerebral cortex. The cellular and molecular mechanisms regulating the specific sequential steps of radial neuronal migration *in vivo* are however still unclear. Recent evidence suggests that distinct signaling cues act cell-autonomously but differentially at particular steps during the overall migration process. Functional MADM (Mosaic Analysis with Double Markers) analyses in comparison to global knockout also indicate a significant degree of cell-non-autonomous and/or community effects in the control of cortical neuron migration. Cell-non-autonomous effects may differentially affect cortical neuron migration in distinct compartments and thus regulate critical steps in the migration process. It is therefore not only essential to determine the nature of the interplay of

cell-autonomous and cell-non-autonomous mechanisms but also how they control cortical neuronal migration. Here we established a MADM-based experimental strategy for the analysis of cell-autonomous versus non-autonomous gene function and/or community effects. We pursued subtractive phenotypic analysis of genetic mosaics (wild-type/heterozygote background) with conditional and/or global knockout (mutant background), both coupled with sparse fluorescent MADM-labeling of homozygous mutant neurons, to trace the sequential steps of migration in 4D. Using these experimental paradigms we define so far unknown cell-autonomous functions of candidate signaling pathways intersecting with cell-non-autonomous effects to coordinate radial neuron migration.

Disclosures: A.H. Hansen: None. **J. Renno:** None. **C. Streicher:** None. **S. Laukoter:** None. **F.M. Pauler:** None. **L. Andersen:** None. **T. Ruelicke:** None. **S. Hippenmeyer:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.03/A31

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01MH110438-NIH/NIMH
R01NS100808-NIH/NINDS

Title: Human forebrain endothelial cells: New avenue for interneuron-based therapy of neuropsychiatric disorders

Authors: *D. DATTA, S. SUBBURAJU, S. KAYE, A. VASUDEVAN
Dept. of Psychiatry, Harvard Med. Sch., Belmont, MA

Abstract: Abnormalities in GABAergic interneurons are implicated in the pathology of severe brain disorders like schizophrenia and epilepsy, for which effective treatments are still elusive. Transplantation of human stem cell-derived interneurons is a promising cell-based therapy for treatment of these disorders. In mouse xenograft studies, human stem cell derived-interneuron precursors could differentiate in vivo, but required a prolonged time (up to seven months) to migrate from the graft site and integrate with the host tissue. This poses a serious roadblock for clinical translation of this approach. For transplantation to be effective, especially for very sick or severe patients, grafted neurons should migrate to affected areas at a faster rate. Our group has previously discovered in mouse that endothelial cells of the periventricular vascular network act as physical substrates, and provide valuable guidance cues for migrating GABAergic interneurons in the developing forebrain. In this study we translated this discovery into human, with significant therapeutic implications. We generated human periventricular endothelial cells, using human pluripotent stem cell technology. We validated molecular, cellular and functional

properties of the derived cells using microarray profiling and cell-based assays. Co-culture of human periventricular endothelial cells with human interneurons showed a significant increase in rate of interneuron migration in vitro. Co-transplantation of human periventricular endothelial cells with human interneurons in adult mouse brain led to faster migration and wider distribution of grafted interneurons, compared to neuron-only transplants. These results establish that human periventricular endothelial cells are critical for long distance migration of human GABAergic interneurons, and pave the way for a novel strategy for effective interneuron transplantation. Co-delivery of human periventricular endothelial cells with human interneurons will accelerate the migration of grafted neurons in diseased brain, leading to faster and effective brain repair. This strategy will facilitate the advancement of interneuron-based cell therapy into a clinical setting and open new avenues for cure of serious neuropsychiatric disorders.

Disclosures: D. Datta: None. **S. Subburaju:** None. **S. Kaye:** None. **A. Vasudevan:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.04/A32

Topic: A.01. Neurogenesis and Gliogenesis

Support: NICHD Grant (P30HD004612 and U54HD087101)
NSF Grant IOB-0924143 to PEP

Title: Reelin- and dab1-expressing superficial dorsal horn neurons co-express lmx1b and migrate together during development

Authors: *G. METTA YVONE, C. L. CHAVEZ-MARTINEZ, P. E. PHELPS
Integrative Biol. and Physiol., UCLA, Los Angeles, CA

Abstract: In the canonical Reelin-signaling pathway, the binding of secreted Reelin to its two receptors, ApoER2 and Vldlr, induces the phosphorylation of the intracellular protein Disabled-1 (Dab1). Phosphorylated Dab1 then activates pathways that regulate neuronal positioning during development. Mice that lack Reelin, both of its receptors, or Dab1 have neuroanatomical defects and exhibit thermal (heat) hyperalgesia and mechanical insensitivity. Previously we found that Reelin and Dab1 neurons are concentrated in nociceptive areas of the adult dorsal horn, specifically laminae I-II, lateral lamina V, and lateral spinal nucleus (LSN). 70% of the Dab1 neurons co-express Lmx1b and therefore are excitatory. Many of the Dab1-Lmx1b neurons are incorrectly positioned in *Reln*$^{-/-}$ mice. Here we examine the Reelin-positive dorsal horn neurons in adult and developing spinal cord. Our data show that most Reelin neurons in the adult laminae I-II co-express Lmx1b and thus are also excitatory. Furthermore, we show that Reelin- and Dab1-positive neurons are discrete subsets of Lmx1b neurons and together account for almost

50% of the adult Lmx1b-labeled superficial dorsal horn neurons. Interestingly, the locations of Reelin and Dab1-positive neurons are both affected by disruption of the Reelin-signaling pathway. We found more Reelin-Lmx1b neurons within IB4-positive area and fewer within the lateral lamina V and LSN of adult *dab1*$^{lacZ/lacZ}$ compared to *dab1*$^{+/+}$ mice. We also characterized the migration of Reelin and Dab1 neurons during development in *dab1*^{lacZ} and *Reln*^{rl} mice, respectively. We found that Reelin- and Dab1-expressing neurons fated for the dorsal horn shared a nearly identical migratory pathway. Although the migration of Reelin cells appeared normal in *dab1*$^{lacZ/lacZ}$, we observed mispositioned Dab1 neurons during embryonic development of *Reln*$^{-/-}$ dorsal horn. Our finding that Reelin- and Dab1-expressing neurons share the same neurotransmitter phenotype is unique and supports a role for Reelin-signaling in specific pain modalities.

Disclosures: G. Metta Yvone: None. **C.L. Chavez-Martinez:** None. **P.E. Phelps:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.05/A33

Topic: A.01. Neurogenesis and Gliogenesis

Support: Synapsy

Title: The role of the microRNA 122 in the migration and maturation of superficial cortical neurons

Authors: *U. TOMASELLO[1], L. DE VEVEY[2], E. KLINGLER[3], J. PRADOS[2], M. NIQUILLE[2], D. JABAUDON[2], V. BORRELL[4], A. DAYER[2]
[1]Univ. De Geneve, Geneve, Switzerland; [2]Univ. of Geneva, Geneva, Switzerland; [3]Basic Neurosci., Univ. of Geneva, Geneve, Switzerland; [4]Inst. of Neuroscience, CSIC, San Juan de Alicante, Spain

Abstract: The cerebral cortex is built by sequential waves of neurogenesis, giving rise to deep and superficial layer neurons. Superficial layer neurogenesis is evolutionarily the most recent and could require a more complex transcriptional control, possibly by non-coding RNAs such as microRNAs. This hypothesis is supported by the fact that a variety of microRNAs are expressed in pallial progenitors domain in gyrencephalic species. However, their specific role in regulating transcriptional dynamics of superficial layer neurogenesis is largely unknown. Among potential key players, microRNA-122 is predicted to regulate essential pathways of projection neuron development like Wnt1, Cux1 and MeCP2. Here we investigated the role of miR 122 in the development of superficial layer projection neurons (PNs) by a gain-of-function approach in the mouse model, using *in utero* electroporation. We targeted the dorsal pallium at E14.5 and

overexpressed miR 122 in dorsal progenitors. Its impact on cell cycle dynamics and migration was analysed at several subsequent embryonic time points. Our results indicate that progenitor proliferative and neurogenic programs are largely unaffected by miR 122 overexpression. In contrast, miR 122 overexpression alters the migratory dynamics and the positioning of PNs within the cortical plate. Moreover, the small fraction of neurons that reached their correct laminar position partially lose their superficial layer molecular identity. Ongoing transcriptomic analysis of single-cells overexpressing miR 122 at embryonic and postnatal stages are underway in order to identify the molecular mechanisms through which miR 122 controls neuronal migration and identity.

Disclosures: U. Tomasello: None. **L. De Vevey:** None. **E. Klingler:** None. **J. Prados:** None. **M. Niquille:** None. **D. Jabaudon:** None. **V. Borrell:** None. **A. Dayer:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.06/A34

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant T32HL007627

Title: Mitochondrial trafficking and localization are important for neuronal migration

Authors: *A. K. MYERS, G. CHO, J. A. GOLDEN
Brigham and Women's Hosp., Boston, MA

Abstract: Mitochondrial diseases are best recognized in a variety of muscle disorders; however mitochondrial dysfunction is increasingly being recognized in a host of common neurological disorders affecting the cerebral cortex including neurodevelopmental disorders such as autism and some forms of epilepsy. Given this association with neurodevelopmental disorders, understanding the role mitochondria play in early cortical development, an unexplored area, is necessary to understand the pathogenesis of these disorders. Recent studies have suggested that the intracellular localization of mitochondria influence non-neural cell migration. Our published data indicate this is also true for migrating cortical neurons. In this study, we examined the localization pattern of mitochondria in migrating excitatory neurons and inhibitory neurons and assessed the importance of a mitochondrial trafficking GTPase, Miro1, during neuronal migration. We performed *ex vivo* electroporation to label mitochondria in excitatory and inhibitory neurons in embryonic day (E) 14.5 mouse brains. Additionally, we expressed knockdown plasmids to disrupt mitochondrial trafficking and assessed the resulting impact on excitatory and inhibitory neuronal migration. Our data suggest that excitatory neurons and inhibitory neurons have similar but distinct patterns of mitochondrial localization. Mitochondria

in excitatory neurons predominately localize anterior to the cell body. In contrast, mitochondria are highly dynamic as inhibitory neurons migrate, moving from the rear of the cell to the leading process and back. Further, our data suggests that a knockdown for Miro1 disrupts mitochondrial trafficking and specifically perturbs inhibitory neuron migration, branching dynamics, and mitochondrial localization. Currently, the connection between mitochondria localization and neuronal migration is poorly studied. Our data indicate that impaired mitochondrial localization may impact embryonic brain development, specifically neuronal migration. This, at least in part, may underlie the pathogenesis of mitochondrial-related neurodevelopmental disorders.

Disclosures: A.K. Myers: None. **G. Cho:** None. **J.A. Golden:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.07/B1

Topic: A.01. Neurogenesis and Gliogenesis

Support: SNF Grant 31003A_159795/1
SPUM Grant 33CM30-124101

Title: Erythropoietin signaling regulates neuronal migration in the developing neocortex

Authors: P. E. CONSTANTHIN, A. CONTESTABILE, V. PETRENKO, P. SALMON, *J. Z. KISS
Univ. of Geneva, Dept. of Neurosciences, Geneva, Switzerland

Abstract: Erythropoietin (EPO) is a cytokine hormone that is required for erythroid differentiation and has been proved neuroprotective in both animal experiments and clinical trials. EPO and its receptor (EPOR) have been detected in the developing brain and their expression appears to be timely and spatially regulated. However, apart from a potential effect on neurogenesis, the role of endogenous EPO signalling in brain development remains unknown. Here, we report that EPO as well as EPOR is expressed in the developing somatosensory cortex of the rat during the period of radial migration and that their expression is temporally and spatially regulated. We demonstrate using constitutive and conditional genetic strategies that downregulation of EPOR in late generated layer IV excitatory neurons results in mispositioning and accumulation of these cells in the intermediate zone. While most control cells in this zone exhibited a bipolar shape, knocking down EPOR expression by forced expression of shEPOR significantly increased the number of multipolar cells with branched processes. In addition, a large proportion of shEPOR-overexpressing cells displayed a disoriented Golgi apparatus and a decreased number of cells were exiting the intermediate zone. Confocal time-lapse imaging also showed that downregulating EPOR expression results in an increased proportion of cells with

numerous highly dynamic processes and decreased migratory speed. Together, these observations support the hypothesis that EPO signaling is required for the proper polarization and orienting neurons for radial migration. Knockdown of EPOR during radial migration leads to permanently misplaced cells that fail to integrate correctly in the cortical network. Animals with these migration defects exhibited abnormal somatosensory behaviors later in life. Finally, forced expression of extracellular signal-regulated kinase (ERK), a well-known downstream regulator of EPO signaling, restored the normal migratory phenotype and rescued the behavioral phenotype.
Together, these results show for the first time that appropriate activity of intrinsic EPO signaling is required for proper radial migration of neocortical excitatory neurons.

Disclosures: P.E. Constanthin: None. **A. Contestabile:** None. **V. Petrenko:** None. **P. Salmon:** None. **J.Z. Kiss:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.08/B2

Topic: A.01. Neurogenesis and Gliogenesis

Support: NNSF 31671068
Support from Tsinghua Center for Life Sciences

Title: Zeb1 represses neural differentiation and cooperates with Ctbp2 to dynamically regulate cell migration during neocortex development

Authors: *H. WANG[1,2,3], J. ZHENG[4,2,3], Z. XIAO[1], X. YANG[1], Q. SHEN[2,3]
[1]Sch. of Life Sciences, Tsinghua Univ., Beijing City, China; [2]Sch. of Life Sci. and Technology, Tongji Univ., Shanghai, China; [3]Tongji Hosp., Shanghai, China; [4]Med. School, Tsinghua Univ., Beijing City, China

Abstract: Zinc finger E-box binding homeobox 1 (*Zeb1*) is a key regulator of epithelial-mesenchymal transition and cancer metastasis. Mutation of *Zeb1* is associated with human genetic eye diseases and defective brain development. Here we show that *Zeb1* is expressed in the embryonic cortical neural progenitor cells (NPC) and turned off upon neuronal differentiation to allow proper differentiation and migration of neuronal progeny. We found that altering *Zeb1*'s expression in cortical cells in vivo by in utero electroporation (IUE) affected neuronal differentiation and migration. Surprisingly, overexpression of *Zeb1* did not increase NPC proliferation, but disrupted multipolar-to-bipolar transition and the correct positioning of NPCs and differentiating neurons, leading to severe migration defects and heterotopia bands in the white matter at postnatal stage. By high-throughput sequencing we found that *Zeb1* regulates a

cohort of genes involved in cell differentiation and migration, including *NeuroD1* and *Unc5d*. Interestingly, by IP-MS, we identified that ZEB1 binds to CTBP2 in the embryonic cortex. Binding to CTBP2 is required for ZEB1 to elicit the effect on multipolar-to-bipolar transition but not suppression of *NeuroD1*. These findings provide insights for understanding the complexity of transcriptional regulation during neuronal differentiation.

Disclosures: H. Wang: None. **J. Zheng:** None. **Z. Xiao:** None. **X. Yang:** None. **Q. Shen:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.09/B3

Topic: A.01. Neurogenesis and Gliogenesis

Support: AMED (SRPBS, IR3D, 924651)
AMED-CREST (117597)
KAKENHI JP (16H04670)

Title: Deciphering a calcium-regulated pathway that controls radial migration via excitation-morphogenesis coupling

Authors: *S.-I. HORIGANE[1,2,3], S. TAKEMOTO-KIMURA[1,2,3], S. KAMIJO[3], A. ADACHI-MORISHIMA[3], H. FUJII[3], H. BITO[3]
[1]Dept. of Neurosci. 1, Nagoya University, Res. Inst. of Environme, Nagoya-Shi, Japan; [2]Mol. neuroscience, Nagoya Univ. Grad. Sch. of Med., Nagoya-shi, Japan; [3]Dept. of Neurochemistry, Grad. Sch. of Medicine, The Univ. of Tokyo, Tokyo, Japan

Abstract: During cortical circuit formation, spontaneous Ca^{2+} transients are believed to occur even before sensory inputs stimulate neuronal firings, and preceding studies showed Ca^{2+} signaling regulates several aspects of neuronal development in the embryonic brain. Consistent with these findings, we previously reported that distinct limbs of the CaMKK-CaMKI cascade were specifically implicated in determining the extent of either dendritic or axonal growth. To further study the involvement of Ca^{2+} signaling in cortical circuit formation, we investigated whether Ca^{2+} signaling regulates radial migration of excitatory neurons in the embryonic cortex. At first, we identified CaMKIα as a key regulator for radial migration. CaMKIα was necessary for radial migration, whereas excess CaMKIα kinase activity drastically decelerated migration rate. We also observed spontaneous Ca2+ transients in migrating neurons and inverse correlation between the intracellular Ca^{2+} event frequency and migration rate from GCaMP6s based Ca^{2+} imaging studies. Furthermore, pharmacological studies revealed intracellular Ca^{2+} transients are L-type VDCC dependent. L-type VDCC was necessary for radial migration, whereas L-type

VDCC with Timothy syndrome mutation (G406R), which causes excess Ca^{2+} influx, induced a severe radial migration defect. Finally, chelation of intracellular free Ca^{2+} using EGTA-AM that blocked intracellular Ca^{2+} transients and impaired radial migration. Taken together, these results suggest appropriate temporal pattern of Ca^{2+} transients facilitates radial migration via Ca^{2+} dependent signaling molecules.

Disclosures: S. Horigane: None. **S. Takemoto-Kimura:** None. **S. Kamijo:** None. **A. Adachi-Morishima:** None. **H. Fujii:** None. **H. Bito:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.10/B4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NRF2016R1A2B4011393
Ministry of Siecnce, ICT&Future Planning 18-BR-02-04

Title: A mercaptoacetamide-based class II histone deacetylase inhibitor suppresses cell migration and invasion in monomorphic malignant human glioma cells by inhibiting FAK/STAT3 signaling

Authors: *H. NAM, J. NAM[1], J.-Y. LEE[1], H.-S. HOE[2]
[1]Korea Brain Res. Inst., Daegu, Korea, Republic of; [2]Korea Brain Reserach Inst., Daegu, Korea, Republic of

Abstract: Histone deacetylase inhibitors (HDACIs) have emerged as potential anticancer agents for the treatment of solid and hematopoietic cancers. Several HDACIs delay cell growth, induce differentiation, or activate apoptosis in multiple types of tumors, including glioblastomas. In the present study, we showed that the mercaptoacetamide-based HDACI W2 inhibits cell migration and invasion in monomorphic malignant human glioma cells. W2 treatment significantly decreased the activity and expression levels of matrix metalloprotease-2 in malignant A172 cells but not in U373MG cells. Key signaling pathways involved in cell migration and invasion, including PI3K-AKT, ERK-JNK-P38, and FAK/STAT3, were examined to identify the mechanism of action of W2. W2 increased the phosphorylation of AKT and altered cell migration and invasion in an AKT-independent manner. W2 inhibited the phosphorylation of FAK/STAT3, and treatment with a FAK/STAT3 inhibitor significantly suppressed cancer cell migration and MMP-2 activity in the presence of W2. In addition, W2 significantly inhibited the nuclear translocation of phospho-STAT3. Taken together, our results suggest that W2 suppresses cancer cell migration and invasion by inhibiting FAK/STAT3 signaling and STAT3 translocation to the nucleus in monomorphic malignant human glioma cells.

Disclosures: J. Nam: None. **J. Lee:** None. **H. Hoe:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.11/B5

Topic: A.01. Neurogenesis and Gliogenesis

Support: MOST 103-2911-I-010-504

Title: The role of a novel BICD2 mutation in brain development and lissencephaly

Authors: *H.-Y. CHENG[1], F.-S. NIAN[1], M.-H. TSAI[2], J.-W. TSAI[1]
[1]Inst. of Brain Sci., Natl. Yang-Ming Univ., Taipei, Taiwan; [2]Dept. of Neurol., Kaohsiung Chang Gung Mem. Hosp., Kaohsiung, Taiwan

Abstract: During cerebral cortex development, radial glia cells undergo interkinetic nuclear migration (INM) and proliferate at the ventricular zone. The progeny cells differentiate into neurons followed by radial migration along radial glia fibers to form the organized cerebral cortex. Previous studies have shown that nuclear position during INM requires BicD2, an adapter protein linking dynein motor complex to the nuclear envelope (NE) through binding to a nucleoporin, RAN binding protein 2 (RanBP2). Although BICD2 mutations in humans were associated with spinal muscular atrophy (SMA) but not brain developmental disorders, we recently found a novel BICD2 mutation in a patient with lissencephaly. To understand the role of this mutation in cortical development, we used in utero electroporation to knockdown BicD2 or overexpress wild type (WT) or mutant BicD2 in neural progenitors in mouse embryos and observed the cell distributions several days later. We found that knockdown of BicD2 using shRNA mildly inhibited neuronal migration. Surprisingly, we observed a severe blockage of neuronal migration upon overexpression of our BicD2 mutant while overexpressing WT or three other reported SMA-associated mutations did not affect neuronal migration. Hence our mutation may cause lissencephaly through a dominant negative effect. Furthermore, pulldown assay also showed that our mutation disrupted its interaction to RanBP2, thus interrupting the NE recruitment of Dynein motor complex. Therefore, our BICD2 mutation may cause lissencephaly by disrupting nuclear migration during neuronal migration. Our findings elucidated the novel roles of BicD2 in neuronal migration and lissencephaly pathogenesis and discovered a novel etiology of this severe developmental disorder.

Disclosures: H. Cheng: None. **F. Nian:** None. **M. Tsai:** None. **J. Tsai:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.12/B6

Topic: A.01. Neurogenesis and Gliogenesis

Support: MOST 103-2911-I-010-504

Title: Functions of KBP in neural development and its role in causing Goldberg-Shprintzen syndrome

Authors: *H.-Y. CHANG, C.-W. HUANG, J.-W. TSAI
Inst. of Brain Sci., Natl. Yang-Ming Univ., Taipei, Taiwan

Abstract: Kinesin-binding protein (KBP; KIF1BP; KIAA1279) functions as a regulator of a subset of kinesins, many of which play important roles in neural development. Previous studies have shown that KBP is expressed in nearly all tissue with cytoplasmic localization. Autosomal recessive mutations in *KIAA1279* causes a rare neurological disorder, Goldberg-Shprintzen syndrome (GOSHS), characterized by microcephaly, polymicrogyria, intellectual disability, axonal neuropathy, thin corpus callosum and peripheral neuropathy. Most *KIAA1279* mutations found in GOSHS patients are homozygous nonsense mutations that result in KBP loss of function. However, the mechanism of KBP dysfunction in causing these defects remains not fully understood. Here we used *in utero* electroporation (IUE) to express KBP shRNA with green fluorescent protein (GFP) in radial glial progenitors in embryonic day (E) 14 mice and collected brain slices at different developmental stages. By immunostaining of neuronal lineage markers, we found that neural differentiation process is not affected. However, four days after IUE, KBP knockdown led to many cells arrested in the intermediate zone (IZ) where neural progenitors undergo multipolar-bipolar transition before they start radial migration. Moreover, at postnatal day (P) 6, about one thirds of the cells, which have become mature neurons, remained ectopically in the white matter. For those cells that have reached Layer II/III of the cortex, neurite outgrowth and axon projection was impaired. Our findings indicate that loss of KBP function leads to defects in neuronal migration and morphogenesis, which may be responsible for brain phenotypes observed in GOSHS.

Disclosures: H. Chang: None. **C. Huang:** None. **J. Tsai:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.13/B7

Topic: A.01. Neurogenesis and Gliogenesis

Support: MOST 103-2911-I-010-504

Title: The role of a novel mutation in forkhead box domain protein in brain development and focal cortical dysplasia

Authors: *C. LIU[1], Y.-T. LIU[2], C. CHEN[2], K.-P. CHANG[3], Y.-H. SHIH[2], S.-Y. KWAN[2], H.-H. CHEN[2], J.-W. TSAI[1]
[1]Inst. Of Brain Sci., Natl. Yang-Ming Univ., Taipei, Taiwan; [2]Neurolog. Institute, Taipei Veterans Gen. Hosp., Taipei, Taiwan; [3]Dept. of Pediatrics, Taipei Veterans Gen. Hosp., Taipei, Taiwan

Abstract: Focal cortical dysplasia (FCD) is a heterogeneous form of neurodevelopmental disorders characterized by local cortical malformation. Using next generation sequencing (NGS), we identified a novel gene mutation of Forkhead box (FOX) protein in a family with FCD. This transcription factor contributes to the regulation of cell cycle, proliferation and differentiation. However, the function of this FOX protein in cortical development is unexplored. In this study, we hypothesize that this FOX may play important roles in cortical development through regulating neural progenitor cell proliferation, differentiation and/or migration. We used *in utero* electroporation (IUE) of the FOX shRNA or cDNA into embryonic mouse brains to knock down or overexpress the FOX protein in neural progenitor cells. Neuronal proliferation, differentiation, and migration patterns were then examined later by immunostaining of cell cycle and cell fate markers under a fluorescence confocal microscope. We found that knocking down this FOX protein at embryonic day 14.5 (E14.5) led to a migration delay with more neurons located in the intermediate zone (IZ) 4 days after IUE. At postnatal day 6 (P6), we observed a layer of neurons arrested in deep cortical layer. Interestingly, the percentage of cells positive to the progenitor cell marker Pax6 was increased, suggesting a delay in neuronal differentiation. Furthermore, the cell exit index decreased in the knockdown group, implying this FOX protein might be a possible factor in neurogenesis regulation. Our findings indicate that the dysfunction of this FOX protein impairs the differentiation and migration of neural progenitor cells, which may lead to characteristic abnormal neurons found in FCD lesions.

Disclosures: C. Liu: None. **Y. Liu:** None. **C. Chen:** None. **K. Chang:** None. **Y. Shih:** None. **S. Kwan:** None. **H. Chen:** None. **J. Tsai:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.14/B8

Topic: A.01. Neurogenesis and Gliogenesis

Support: CIHR
CURE Epilepsy
Fonds recherche du Québec-Santé
Fondation des Étoiles
Fondation Ste-Justine
Brain Canada
Health Canada

Title: Delayed GABAergic interneuron migration through impaired actin remodelling in a mouse model with deletion of the autism gene MYO9B

Authors: *L. EID[1,2], P. K. R. PEDABALIYARASIMHUNI[1,2], L. MARCOUX[1], X. JIANG[1,2], A. LUPIEN-MEILLEUR[1,2], L. TOUSSAINT[1,2], M. LACHANCE[1], J.-C. LACAILLE[2], G. HICKSON[1,3], E. ROSSIGNOL[1,4]
[1]Ctr. de Recherche du CHU Sainte-Justine, Montreal, QC, Canada; [2]Neurosci., [3]Pathology and Cell. Biol., [4]Neurosci. and Pediatrics, Univ. de Montréal, Montréal, QC, Canada

Abstract: Autism spectrum disorders (ASD) are genetically heterogeneous. Recent data suggest that a subset of genetically-determined ASD result from defects in the development of inhibitory GABAergic interneurons (INs), leading to aberrant enhancement of cortical excitability. *De novo* mutations in the *MYO9B* gene, encoding a non-muscular myosin with a RhoA-specific RhoGAP domain, have recently been associated with ASD. *Myo9b* regulates dendritogenesis in pyramidal cells (PCs) and is involved in cell motility in other cellular populations, including osteoclasts and dendritic immune cells. However, its roles in brain development, including in the migration and maturation of INs, are unknown. Given the central role of RhoA in actin remodeling and in IN maturation, and the implication of IN pathologies in ASD, we hypothesized that *Myo9b* might be a central regulator of IN development. We thus generated *Nkx2.1^{Cre};Myo9b$^{c/c}$* mutant mice, carrying a conditional deletion of *Myo9b* in MGE-derived INs. We find that the morphology of migrating INs is disrupted at e13.5 in mutant mice, with excessively elongated and branched processes, resulting in a delay in tangential migration that persists at P3 but resolves by P21. Furthermore, time-lapse imaging of F-actin (*Lifeact*) in INs migrating from MGE explants reveals an increased meandering, with slower and infrequent nukleokinesis, resulting in reduced net displacement of mutant INs. Also, we note a more diffuse F-actin distribution in the soma of mutant INs, suggesting a reduction in actin turnover. Immunostaining and western blot analyses

indicate that this is in part attributable to an increased phosphorylation of cofilin, the actin-severing enzyme downstream of RhoA. Altogether, our data suggest that *Myo9b* is a critical player regulating IN development, possibly through its repression of RhoA signaling, and that its loss prevents actin remodeling and perturbs IN migration. In turn, this delay in tangential migration might impact the establishment of neuronal networks during early post-natal ages and lead to socialization deficits and other cognitive impairments seen in patients with *MYO9B*-associated ASD.

Disclosures: L. Eid: None. **P.K.R. Pedabaliyarasimhuni:** None. **L. Marcoux:** None. **X. Jiang:** None. **A. Lupien-Meilleur:** None. **L. Toussaint:** None. **M. Lachance:** None. **J. Lacaille:** None. **G. Hickson:** None. **E. Rossignol:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.15/B9

Topic: A.01. Neurogenesis and Gliogenesis

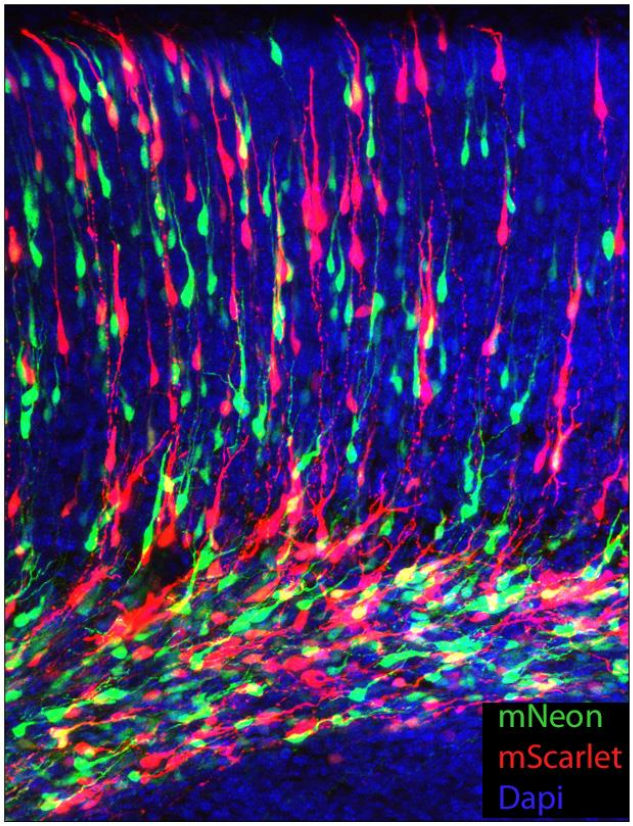
Support: NIH R01-NS080928-04
NIH T32-GM007507

Title: Determining the role of neurite initiation *in vivo* using a novel labeling approach to *in utero* electroporation

Authors: *R. J. TAYLOR[1], K. L. TAYLOR[2], J. CARRINGTON[2], M. MCDERMOTT[2], K. RICHTERS[2], E. W. DENT[2]
[1]Univ. of Wisconsin Madison, Madison, WI; [2]Neurosci., Univ. of Wisconsin, Madison, WI

Abstract: Neurite initiation from a newly born neuron is a critical step in neuronal differentiation. We have previously described the unique role of Cdc42-Interacting Protein 4 (CIP4) in the inhibition of neurite initiation *in vitro*. However, the role of CIP4 in neuronal migration and neurite initiation *in vivo* have not yet been evaluated. Within the prenatal cortex CIP4 protein levels track directly with neuronal migration. CIP4 is expressed highly prenatally, during the period of active neuronal migration in cortex, but decreases to undetectable levels just after birth, when neurons have ceased migrating. To determine the role of CIP4 in cortical neuron migration and neurite initiation we have developed a novel approach for labeling both control and knockdown/overexpressing neurons after *in utero* electroporation (IUE). This technique results in internal controls and experimentally manipulated neurons to be generated in a single brain, obviating the need for separate control and experimental IUEs and subsequent matching of brain sections. Using this new labeling approach, termed Double UP, we have both prematurely decreased CIP4 expression and artificially maintained CIP4 expression beyond

when it would normally decrease. Preliminary experiments indicate that decreasing CIP4 expression causes precocious migration, while maintaining CIP4 expression at high levels delays cortical neuron migration, neurite initiation and axonal extension across the midline. Implementation of this powerful labeling technique will allow for more accurate comparison between experimental and control conditions and requires fewer experiments, saving time and resources.



In Utero Electroporation of Double UP
Cortical section through an embryonic brain of an e17.5 mouse, which recieved Double UP and limiting amounts of Cre plasmid at e14.5.

Disclosures: R.J. Taylor: None. **K.L. Taylor:** None. **J. Carrington:** None. **M. McDermott:** None. **K. Richters:** None. **E.W. Dent:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.16/B10

Topic: A.01. Neurogenesis and Gliogenesis

Title: The effects of mutant Pea3 on cell invasion and cell migration

Authors: *M. USTUN, I. KURNAZ
Gebze Tech. Univ., Kocaeli, Turkey

Abstract: ETS domain transcription factors that contain specific common purine rich DNA sequence in all family members regulate numbers of cellular genes being critical for many celular process. Pea3/ETV4 transcription factor which is ETS family member known to be regulated by many growth factors through MEK/ERK (MAPK) signal transduction cascade during neural development. In this study, our goal is to understand the effects of putative Pea3 phosphorylation sites on cell invasion and cell migration under the conditions of several growth factors. Mimicking and silencing mutations on putative MAPK phosphorylation sites on mPea3 were created by SiteDirected Mutagenesis. The mutant mPea3 plasmids were transfected into the SHSY5Y human neuroblastoma cells and their protein expression levels were analyzed by Western Blot Analysis, transfected cells were also induced with diverse growth factors by cell culture techniques and the protein expressions were checked. Finally, morphological analysis of growth factor induced cells that include mutant mPea3 have been proceed by Immunofluorescence. Various growth factors are known to regulate Pea3 members at the different stages of development. Studies also show that Pea3 leads to dendritic arborization of motor neurons and retinal ganglion cells in response to diverse growth factors. As supported with our experiments, Pea3 induces axonal growth in various neural model cells, and the protein expression pattern of mutant mPea3s with/without growth factors was diverse. The elucidation of Pea3 activation would be contributed to understand of neuroregeneration mechanism after axonal injuries or nerve crush injuries which trigger the retrograde signaling for proper regeneration.

Disclosures: M. Ustun: None. **I. Kurnaz:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.17/B11

Topic: A.01. Neurogenesis and Gliogenesis

Support: Departmental Initial Complement Funds, University of California Riverside

Title: Developmental and physiological defects in a mouse model of cobblestone lissencephaly

Authors: *W. WONG[1], Y. C. WONG[1], C. R. JONAK[3], D. K. BINDER[3], E. ZAGHA[2], M. M. RICCOMAGNO[1]
[1]Molecular, Cell, and Systems Biol., [2]Psychology, Univ. of California, Riverside, Riverside, CA; [3]Biomed. Sci., Univ. of California, Riverside Sch. of Med., Riverside, CA

Abstract: We aim to identify the role of a family of adaptor proteins during neocortical lamination and cortical circuit establishment. During neocortical development, migrating neurons must accurately interpret signaling cues to laminate properly. The Crk-associated substrate (*Cas*) family of cytosolic signaling adaptor proteins mediates cellular responses to neural guidance cues, making them good candidates to integrate multiple signaling pathways. Cas adaptor proteins show strong and specific expression in the cortical plate and white matter, in a manner consistent with playing a role in radial migration and stratification during neural development. We used a conditional gene targeting approach to inactivate neocortical expression of three embryonically expressed Cas proteins (p130Cas, CasL, and Sin). Cas triple conditional knockout (*CasTcKO*) mice display severe cortical phenotypes resembling cobblestone lissencephaly. A hallmark of the debilitating neurodevelopmental disorder in our mouse model includes ectopic clusters of neurons migrating beyond the marginal zone and invading the meninges. *CasTcKO* brains have L1+ axon bundles innervating these ectopias and display mispositioned deep layer and superficial layer neurons. These findings support the notion that Cas adaptor proteins play essential roles during neural migration and circuit formation. To explore the physiological correlates of these lamination defects, we performed electroencephalography (EEG) recordings and trained mutant and control animals in a Go/No-Go somatosensory detection task. EEG analysis revealed the presence of epileptiform activity in the frontal and somatosensory cortices of *CasTcKO* mutant mice, which are absent in control animals. Furthermore, *CasTcKO* animals performed poorer in the detection task. Intriguingly, mutant mice demonstrated long periods of disengagement during the task, which may correlate with the electroencephalographic abnormalities. Our study provides unique and significant mechanistic insight into how the neocortex forms and how neurodevelopmental disorders may arise.

Disclosures: W. Wong: None. **Y.C. Wong:** None. **C.R. Jonak:** None. **D.K. Binder:** None. **E. Zagha:** None. **M.M. Riccomagno:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.18/B12

Topic: A.01. Neurogenesis and Gliogenesis

Title: Prenatal exposure to opioids and neurodevelopmental toxicity in the developing chicken embryo model

Authors: *M. HADERA[1], J. M. ANDERSEN[1,2], R. E. PAULSEN[1]
[1]Dept. of Pharmaceut. Biosci., Univ. of Oslo, Sch. of Pharm., Oslo, Norway; [2]Dept. of Forensic Sci., Oslo Univ. Hosp., Oslo, Norway

Abstract: Introduction: Methadone is used in opioid maintenance therapy during pregnancy, though reports indicate potential for long-term neurodevelopmental deficits in exposed children. The mechanisms by which it influences neurodevelopment is not yet known but opioid systems appear early in neurogenesis and are believed to play roles during the neurodevelopment process. The developing chicken embryo is an attractive model system with potential for nonclinical safety studies of pharmaceuticals. The ontogeny of the opioid system is well characterized in this model and reflects the development in rodents as well as humans. In this study we aimed to explore the effect of methadone and morphine on some markers that are known to represent aspects of the neurodevelopment in the cerebellum. **Methods:** On embryonic day (ED) 13 (single exposure) or ED13 and 16 (repeated exposure), methadone and morphine at 20 mg/kg dose were injected onto the chorioallantoic membrane of chicken (*Gallus gallus*) embryos. On ED17, embryos were anesthetized by hypothermia, hatched, decapitated and then the cerebellum harvested. Protein expression of PAX6, MMP9, NR2B (neuronal migration markers) and PCNA (proliferation marker) was analyzed using western blotting. We also studied the effect on PAX6 promotor activity in primary cultures of cerebellar granule neurons from E17 chicken. We included both untreated control as well as vehicle (saline) controls in all the experiments. The data is obtained from 6-9 independent observations and results represent average effects on male and female cerebellum. **Results:** There were no significant differences between the untreated and saline treated groups. We observed reduced levels of PAX (30%; One-way ANOVA, P=0.005) and MMP9 (40%; P=0.04) in the methadone treated compared to the control in the ED13 injected embryos. Though not significant, a 25% reduction in level of NR2B was also observed in the same comparison. Methadone injection on ED13 did not affect PCNA expression. We did not see statistically significant changes in any of the markers in the morphine treatment in the ED13 protocol. None of the treatments showed effects in the ED13 and ED16 repeated injection protocol. Neither morphine nor methadone affected PAX6 promotor activity. **Conclusion**: The developing chicken embryo is a promising alternative animal model for testing of effects by medications on neurodevelopment. Methadone appears to affect molecular markers of migration

of cerebellar granule neurons in this model and it will be interesting to explore histologic changes associated with the observed effects.

Disclosures: M. Hadera: None. **J.M. Andersen:** None. **R.E. Paulsen:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.19/B13

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant DA02399
NIH Grant EY002593

Title: Metabolic regulation and glucose sensitivity of cortical radial glial cells

Authors: *B. G. RASH[1], N. MICALI[1], A. J. HUTTNER[1], Y. M. MOROZOV[1], T. L. HORVATH[2], P. RAKIC[3]
[1]Dept. of Neurosci., [2]Section of Comparative Med., [3]Dept. of Neurosci. and Kavli Inst. for Neurosci., Yale Univ., New Haven, CT

Abstract: The primary stem cells of the cerebral cortex are the radial glial cells (RGC)s, and disturbances in their operation lead to myriad brain disorders in all mammals from mouse to human. Yet, their physiology and metabolic sensitivities are not well understood. Here we found in mice that maternal gestational obesity and hyperglycemia can delay RGC neurogenesis and impair neuronal migration to the cortical plate. Using optogenetic approaches we found that Ca^{2+} signaling regulates mitochondrial transport and is crucial for metabolic support in RGC fibers. Cyclic intracellular Ca^{2+} discharge from localized RGC fiber segments detains passing mitochondria and ensures their proper distribution and enrichment at specific sites such as endfeet. Impairment of mitochondrial function caused an acute loss of Ca^{2+} signaling, while hyperglycemia decreased Ca^{2+} activity and impaired mitochondrial transport, leading to degradation of the RGC scaffold. Our findings therefore uncover a novel physiological mechanism indicating pathways by which gestational metabolic disturbances can interfere with brain development. Furthermore, we found that elevated slow-wave Ca^{2+} activity is a feature of cortical neural stem cells (NSCs), but not human induced pluripotent stem cells. Our data support the hypothesis that multiple types of Ca^{2+} activity regulate NSC function and neurogenesis during cortical development, but other stem cell types utilize different regulatory mechanisms for cell type differentiation.

Disclosures: B.G. Rash: None. **N. Micali:** None. **A.J. Huttner:** None. **Y.M. Morozov:** None. **T.L. Horvath:** None. **P. Rakic:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.20/B14

Topic: A.01. Neurogenesis and Gliogenesis

Support: U01MH105989

Title: Developing lineages of the human cerebral cortex

Authors: *T. NOWAKOWSKI[1], A. BHADURI[2], A. A. POLLEN[2], R. DELGADO[4], G. SCHMUNK[6], B. ALVARADO[5], M. MOSTAJO-RADJI[5], E. DI LULLO[5], C. SANDOVAL-ESPINOSA[5], M. HAEUSSLER[7], J. W. KENT[7], A. R. KRIEGSTEIN[3]
[1]Broad Ctr. of Regeneration Med. and Stem Cell Res., [3]Eli and Edythe Broad Ctr. for Regeneration Med. and Stem Cell Res., [2]Univ. of California San Francisco, San Francisco, CA; [4]Anat., [5]UCSF, San Francisco, CA; [6]Regeneration Med., Univ. of California, San Francisco, San Francisco, CA; [7]UCSC, Santa Cruz, CA

Abstract: Human cerebral cortex consists of billions of neurons distributed across dozens of functional areas. Using unbiased single cell capture and RNA sequencing, we sought to characterize the diversity of molecular programs underlying the differentiation of specialized cell types in the developing human forebrain. We uncover a highly conserved neuronal differentiation signature shared across forebrain regions, as well as specialized signatures characteristic of ventral and dorsal telencephalon. Within the cortex, we discover an unexpected diversity of excitatory pyramidal neuron lineages that relates strongly to cortical area of origin, but poorly reflects adult cortical layer signatures. By relating these area specific signatures to differentiation states our analysis reveals a limited number of transcriptomic differences among progenitor cells cascades into robust typological differences among maturing excitatory neurons. By analyzing the molecular diversity of radial glia progenitor cells, we discover the molecular signatures related to classical radial glia, characterized by the expression of proneural transcription factors, and outer radial glia, and a distinct signature of radial glia at the ventricular zone which emerges mid-way through neurogenesis. We investigated the emergence of this cell type in primary tissue samples by labelling their morphology and found an unexpected transition from classical pial surface-contacting radial glia to shorter, "truncated" morphologies that coincide with the emergence of this transcritomic state. This transcriptomic-based classification of radial glia in the human cerebral cortex suggests a revised model of cortical development as it applies to primates. The model accounts for the transformation of the radial glia scaffold from a physically continuous to the physically discontinuous structure, and accounts for the disproportionate expansion of the supragranular layers in primate species.

Disclosures: T. Nowakowski: None. **A. Bhaduri:** None. **A.A. Pollen:** None. **R. Delgado:** None. **G. Schmunk:** None. **B. Alvarado:** None. **M. Mostajo-Radji:** None. **E. Di Lullo:** None. **C. Sandoval-Espinosa:** None. **M. Haeussler:** None. **J.W. Kent:** None. **A.R. Kriegstein:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.21/B15

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSFC31371093

Title: Temporal specific regulation of neural differentiation by Foxg1 in the developing cerebral cortex

Authors: Q.-R. BAI[1], *Q. SHEN[2]
[1]Tongji Univ., Shanghai, China; [2]Sch. of Life Sci. and Technol., Tongji Univ., Shanghai City, China

Abstract: Neural stem cells in the embryonic mammalian brain are located in the germinal zones along the ventricular surface and play fundamental roles in generating diverse cell types on a precisely timed schedule. Understanding the intrinsic timing mechanism is important for directed differentiation of neural stem cells to obtain desired cell types for therapeutic use. Previous studies have shown that Foxg1, a forebrain specific transcription factor, regulates the timing sequence of cortical neuron generation, however its molecular mechanism is still not clear. Here using chromatin-immunoprecipitation followed by sequencing analysis we performed genome-wide mapping of Foxg1 binding sites in FACS-selected cortical neural progenitor cells at different stages during embryonic development. We found that Foxg1 is dynamically distributed in the genome of neural stem and progenitor cells, binding to different targets at different developmental stages. In combination with RNA-seq analysis of stage-specific gene expression of FACS-purified neural progenitor cells, we identified putative Foxg1-regulated gene networks. We are confirming potential targets regulated by Foxg1 through analyzing changes in gene expression profile after conditional deletion of Foxg1 in cortical progenitor cells. Furthermore, we found that Foxg1 binding motifs are highly associated with other transcription factors that are important for neural differentiation, and confirmed their interactions in cell lines. Our findings suggest that Foxg1 acts as a master regulator of the timing mechanism controlling neural stem cell differentiation during cortical development.

Disclosures: Q. Bai: None. **Q. Shen:** None.

Poster

637. Neural Cell Migration and Lineage Specification

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 637.22/B16

Topic: A.01. Neurogenesis and Gliogenesis

Title: The roles of tri-methylation of histone h3 lysine 27-mediated pathways in neurodevelopment

Authors: *C. LIU, P.-P. LIU, Y.-J. XU, G.-B. TANG, H.-Z. DU, S.-K. DAI, Z.-Q. TENG
The State Key Lab. of Stem cell and Reproductive Biol., Inst. of Zoology, Chinese Acad. of Sci., Beijing, China

Abstract: Histone H3K27 exists in three methylation states, monomethylated (H3K27me1), dimethylated (H3K27me2), and trimethylated (H3K27me3), a mark of transcriptionally silent chromatin. Evidence shows that polycomb repressive complex 2 (PRC2) localizes with H3K27me3 and has histone methyltransferase activity and primarily trimethylates histone H3 on lysine 27 (H3K27me3). Reduction of H3K27me3 can be accomplished by active H3K27me3 demethylation mediated by H3K27me2/3 demethylases in mammals. These enzymes include UTX /KMD6A (lysine demethylase 6A) and JMJD3/KDM6B, both of which contain a JmjC (Jumonji) catalytic domain for de-methylation of H3K27me3. What's more, Clinical data and sequencing information show that constitutional loss-of-function defects in PRC2 components (EZH2, EED) and UTX cause Weaver syndrome and Kabuki syndrome separately, which are both characterized by moderate-to-severe congenital anomaly/mental retardation. To investigate the mechanism underlying these diseases, we systematically studied the roles of H3K27me3-mediated signalings in neural development. Firstly, we show that miR-203 is repressed by PRC2 in both embryonic and adult in neural stem/progenitor cells (NSPCs). MiR-203 negatively regulates the proliferation of NSPCs. One of PRC1 components, Bmi1, is a downstream target of miR-203 in NSPCs. this study provides the first evidence for coordinated function of the EZH2-miR-203-Bmi1 regulatory axis that regulating the proliferation of NSPCs(Liu, Tang et al. 2017). We also found that EED (embryonic ectoderm development), the core component of PRC2, is necessary for maintenance of the NSPC pool, especially during neurogenesis in the early postnatal DG, which established a critical role of EED in hippocampal DG development (in revision). To our surprise, our results demonstrate that deletion of UTX in the brains of both developing and adult mice results in increased anxiety-like behaviors and impaired spatial learning and memory. Loss of Utx in the hippocampus leads to reduced long-term potentiation (LTP), amplitude of miniature excitatory postsynaptic currents (mEPSCs), aberrant dendrite development, and defective synapse formation(Tang, Zeng et al. 2017). Therefore, we hypothesized that PRC2 has emerging roles in the central nervous system(Liu, Xu et al. 2017). Taken together, our results suggest that H3K27me3 signaling and its related enzymes have

critical roles in mediating neural and behavioral plasticity in mice. EZH2, EED and UTX deficiency leading to neural stem cell and cognition deficits may provide the basis for underlying intellectual disability in Weaver Syndrome or Kabuki syndrome.

Disclosures: C. Liu: None. **P. Liu:** None. **Y. Xu:** None. **G. Tang:** None. **H. Du:** None. **S. Dai:** None. **Z. Teng:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.01/B17

Topic: A.04. Transplantation and Regeneration

Support: R01NS092847
R01NS094218
S10OD021624
IK2RX002013

Title: 3D bioengineered neural tissue to mitigate acute cerebral inflammation after brain transplantation in rats

Authors: *V. LIAUDANSKAYA[1], D. JGAMADZE[2], A. N. BERK[1], D. J. BISCHOFF[1], B. J. GU[2], H. HAWKS-MAYER[1], M. J. WHALEN[3], H. I. CHEN[2], D. L. KAPLAN[1]
[1]Biomed. Engin., Tufts Univ., Medford, MA; [2]Neurosurg., Univ. of Pennsylvania, Philadelphia, PA; [3]Neurosci. Ctr. at Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Introduction: Cancer, stroke and other neurodegenerative diseases lead to neural tissue loss, and disrupted neuronal signaling. Current approaches of dissociated stem cell transplantation showed promising results, however has limits for the treatment of large size defects. Thus alternative methods are needed, such as implantation of engineered neural tissues. However, inflammation is a prominent concern in neuronal grafting studies. Neuroinflammation is a critical defense mechanism of the brain, and also modulates tissue regeneration in the diseased state. Thus, a fine balance is required to modulate the inflammatory responses for optimal graft integration and survival. The goal of this study was to design a brain implant to control the local environment in order to mitigate acute inflammation post-implantation *in vivo* to improve graft survival. We pursued rat motor cortex implantation of 3D engineered brain constructs (later in text referred to as implants) loaded with corticosteroid and studied the effect of acute inflammation on graft survival.
Methods: Implants were prepared by seeding E18 rat GFP cortical neurons on silk fibroin scaffolds, followed by embedding in a fibrin hydrogel with/out methylprednisolone (MP, 8.7mM). Constructs were implanted into a motor cortex cavity created by aspiration (2x2mm)

and covered with a fibrin gel +/- MP (Tufts IACUC, M2015-28; University of Pennsylvania IACUC, 805600). Three days post-implantation (3 dpi), animals were perfused, and brains were extracted for analysis of graft viability and inflammatory response.
Results and discussion: MP-loaded implants showed increased survival compared to controls (without MP) 3dpi. Increased survival correlated with decreased levels of pro-inflammatory cytokines (IL-1β, IL-6, TNFα, CCL2 and TIMP1) and a shift of immune cells from a pro-inflammatory towards an anti-inflammatory state with upregulation of CD163, IL-4 and IL-10 expression. CCL2 was a critical contributor to neuronal death during acute inflammation, regulated through the NF-κB pathway and STAT transcriptional factors. Finally, the co-activation of Notch1, STAT3, and NF-κB pathways in MP implants suggested the presence of reactive astrocytes at the site of injury. Overall, we achieved improved survival of MP-loaded implants during the acute phase of inflammation through downregulation of upstream targets for many inflammatory cytokines.

Disclosures: V. Liaudanskaya: None. **D. Jgamadze:** None. **A.N. Berk:** None. **D.J. Bischoff:** None. **B.J. Gu:** None. **H. Hawks-Mayer:** None. **M.J. Whalen:** None. **H.I. Chen:** None. **D.L. Kaplan:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.02/B18

Topic: A.04. Transplantation and Regeneration

Support: 1R44EY027654-01A1

Title: Connectivity of human organoid-derived retinal tissue transplanted into subretinal space of a large-eye animal (cat)

Authors: *I. O. NASONKIN[1], R. K. SINGH[1], L. OCCELLI[2], O. CUZZANI[1], F. BINETTE[1], G. S. HOGGE[1], S. PETERSEN-JONES[2]
[1]BioTime, Inc., Alameda, CA; [2]Small Animal Clin. Sci., Michigan State Univ., East Lancing, MI

Abstract: The conceptual approaches to restoring vision impacted by degenerative retinal diseases or trauma have been enriched by the introduction of 3-dimensional (3D) retinal tissue idea a patch idea, which brings incremental improvements in restoring vision. Compared to Retinal Pigment Epithelium (RPE) layer, which serves an important supportive role in visual process and can benefit from a simple cell suspension-based delivery into the subretinal space, neural retina is a multilayered sensory tissue, which vitally depends on preserving structure and photoreceptor directionality to carry out visual function. To develop bioprosthetic approaches to neural retina repair, we derived 3D human retinal tissue (retinal organoids) from human

embryonic stem cells (HESCs) and investigated delivery, survival and integration of laboratory-grown retina in a large-eye animal model. Human embryonic stem cell-derived retinal tissue was introduced into the subretinal space of wildtype cats using a transvitreal approach following a pars plana vitrectomy (n=7 eyes). *Per os* (orally introduced) prednisone was given at an anti-inflammatory dose for the duration of the study. Cats received either no systemic cyclosporine immunosuppression (n=3 grafts) or continuous systemic cyclosporine (n=4 grafts) starting from seven days before transplantation and then continuously. Eyes were examined by fundoscopy and spectral domain optical coherence tomography (SD-OCT) for adverse effects due to subretinal graft presence or/and surgical procedure and monitored regularly by fundoscopy and SD-OCT. Cats were euthanized 5 weeks following grafting, and immunohistochemistry of retinal sections performed using human-specific antibodies (HNu, Ku80, SC121), axonal, synaptic, retinal cell type-specific markers and lymphocyte, microglia/macrophage markers. We report substantial improvement in the survival of xenogenic retinal tissue grafts in cat subretinal space with systemic immunosuppression protocol and evidence of structural and axonal/synaptic integration. Specifically, we observed SC121-positive, CALB2-positive human axons emanating from the grafts and migrating past the photoreceptor layer of the recipients and ending up in cat's inner nuclear layer and ganglion cell layer. Further refinement of the surgical delivery approaches coupled with improved design of bioprosthetic retina is expected to incrementally improve methods of retinal tissue replacement enabling development of more realistic approaches of restoring vision.

Disclosures: I.O. Nasonkin: A. Employment/Salary (full or part-time):; BioTime, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioTime, Inc. **R.K. Singh:** A. Employment/Salary (full or part-time):; BioTime, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioTime, Inc.. **L. Occelli:** None. **O. Cuzzani:** A. Employment/Salary (full or part-time):; BioTime, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioTime, Inc. **F. Binette:** A. Employment/Salary (full or part-time):; BioTime, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioTime, Inc. **G.S. Hogge:** A. Employment/Salary (full or part-time):; BioTime, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioTime, Inc. **S. Petersen-Jones:** 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.; BioTime, Inc..

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.03/B19

Topic: A.04. Transplantation and Regeneration

Support: DP2EY024504-01
KF-53233
13-SSP-105

Title: Precocious deposition of perineuronal nets on parvalbumin inhibitory neurons transplanted into adult visual cortex

Authors: *D. FIGUEROA VELEZ[1], K. BRADSHAW[2], M. HABEEB[2], S. P. GANDHI[3]
[1]Neurobio. & Behavior, Univ. of California, Irvine, Irvine, CA; [2]Univ. of California Irvine Dept. of Neurobio. and Behavior, Irvine, Irvine, CA; [3]Neurobio. and Behavior, Univ. of California Irvine Dept. of Neurobio. and Behavior, Irvine, CA

Abstract: The end of the critical period for primary visual cortex (V1) coincides with the deposition of perineuronal nets (PNN) onto Parvalbumin (PV) inhibitory neurons. Recently, we found that transplantation of embryonic inhibitory neurons into adult V1 reinstates a new critical period. Here we used Wisteria Floribunda Agglutinin (WFA) staining to compare the deposition of PNNs onto neurons during normal development and following transplantation at equivalent cell ages. In accord with previous findings, PV and PNN expression increases from negligible levels at postnatal day 14 (P14) to mature levels by P70. In contrast to P14, PNNs are found on transplanted neurons by 21 days after transplantation. Moreover, PNN levels remain stable from 21 to 105 days after transplantation. This precocious deposition was specific to PV neurons and excluded transplanted neurons expressing Somatostatin. Notably, the onset of PV expression in transplanted inhibitory neurons follows the timing of PV expression in juvenile V1. Moreover, transplantation has no discernible effect on host PNNs. The precocious deposition of PNNs onto transplanted PV neurons suggests that PNN expression identified by WFA does not reflect neuronal maturity and may be an inaccurate marker for transplant-induced plasticity of cortical circuits.

Disclosures: D. Figueroa Velez: None. **K. Bradshaw:** None. **M. Habeeb:** None. **S.P. Gandhi:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.04/B20

Topic: A.04. Transplantation and Regeneration

Support: Children's Mercy Hospital
The Ronald D. Deffenbaugh Foundation
Kansas Intellectual and Developmental Disabilities Research Center grant HD090216

Title: Transplanted neural progenitor cell survival and development in a jaundiced rat model of kernicterus

Authors: *F.-C. YANG[1], J. VIVIAN[2], S. M. SHAPIRO[3], J. A. STANFORD[1]
[1]Dept. of Mol. and Integrative Physiol., [2]Dept. of Pathology & Lab. Med., Univ. of Kansas Med. Ctr., Kansas City, KS; [3]Pediatrics, Children's Mercy Hosp. & Clinics, Kansas City, MO

Abstract: Neonatal hyperbilirubinemia targets specific brain nuclei and can lead to kernicterus. The most debilitating symptom of kernicterus is dystonia, caused by bilirubin toxicity in GABAergic neurons of the globus pallidus (GP). We believe that targeting GP with neuronal stem cells is a promising therapeutic approach to treat dystonia in kernicterus. We have reported greater neuronal progenitor cell (NPC) survival in brains of jaundiced (jj) than non-jaundiced (Nj) Gunn rats. The goal of the current study was to further determine NPC survival and development in a more severe condition of bilirubin toxicity that closely resembles kernicterus in human cases. For this purpose, we modified the model by injecting sulfadimethoxine (sulfa, 50 or 70mg/kg) to jj rats at postnatal day 10 (P10). These rats and their Nj littermates then received inhibitory medial ganglion eminence neuron-like (MGE-like) NPCs grafted unilaterally to the GP at P21. Immunosuppressant cyclosporine A was given after transplantation throughout the experiment. Animals were allowed to survive 3 weeks or 7 weeks after the surgery. Brain sections were processed with immunohistochemical analyses to identify cell survival, cell properties and fiber outgrowth. Our preliminary data suggests: 1. Even after hyperbilirubinemia exacerbation (sulfa treatment), jj rat brains (7 weeks or 3 weeks) still had greater graft cell survival than Nj rat brains. 2. There were more mature graft cells in brains of 7-week group than in 3-week group. 3. Overall, necrotic tissue was relatively low all groups, maybe due to immunosuppressant, which we did not use in our previous studies. We observed fewer necrotic cells in brains of 7-week group compared to 3-week group. Interestingly, Nj brains had more necrotic tissue than jj brain. 4. Abundant fiber outgrowth was identified in all cases. Fibers distributed widely from the injection site. While a type of short, parallel fibers were concentrated near the core of the graft, many long fibers projected ventromedially from the GP. 5. PENK (proenkephalin)-ir graft cells exited from the graft site, but they were few and immature. 6. We

previous reported that NPC graft induced strong PENK expression in certain cells (possibly astrocytes) surrounding the graft in the host brain. In this experiment we found the PENK expression was much weaker 7 weeks after transplantation in both jj and Nj brains. In conclusion, MGE-like NPCs were able to survive and generate various types of fibers in more severely bilirubin-damaged brains, supporting the feasibility of stem cell therapy in kernicterus.

Disclosures: F. Yang: None. **J. Vivian:** None. **S.M. Shapiro:** None. **J.A. Stanford:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.05/B21

Topic: A.04. Transplantation and Regeneration

Support: JSPS KAKENHI grant number 26462168
Merit Review Award 1 I01 BX003190 from the U.S Department of Veterans Affairs Biomedical Laboratory Research and Development Service and the Rehabilitation and Research and Development Service

Title: Functional recovery after the systemic administration of mesenchymal stem cells in a rat model of neonatal hypoxic-ischemia

Authors: *T. SAKAI[1,2], M. SASAKI[2], Y. KATAOKA-SASAKI[2], S. OKA[2], M. NAKAZAKI[2], S. FUKUMURA[2], M. KOBAYASHI[2], H. TSUTSUMI[2], J. D. KOCSIS[3], O. HONMOU[2]
[1]Tomakomai City Hosp., Tomakomai / Hokkaido, Japan; [2]Sapporo Med. Univ., Sapporo / Hokkaido, Japan; [3]Neurosci. Res., Yale Univ. Sch. Med., West Haven, CT

Abstract: ***Objective:*** Children who have experienced neonatal hypoxic-ischemic encephalopathy often develop cerebral palsy. Although many treatments have been performed, few effective therapies are available. In this study, we tested the hypothesis in rats with hypoxia-ischemia (HI) injuries that the systemic infusion of mesenchymal stem cells (MSCs) would result in functional improvement by facilitating neural compensation in the contralesional cortex.
Methods: Postnatal (P) day 7 (P7) rats that had undergone unilateral hemisphere hypoxia-ischemia (modified Rice-Vannucci model) were randomly assigned to MSC-infused or vehicle-infused groups. MSCs (1.0×10^6/200 μL) or vehicle were intravenously infused at P10. Brain volume was measured using *in vivo* magnetic resonance imaging (MRI) on P8 and P35. On P35, the rats were sacrificed after their behavior was evaluated using a beam walk test, and their brains were then prepared for histological analyses.
Results: The MSC-treated group had less slips on the beam walk test compared to those in the vehicle group ($p = 0.041$). MRI was used to measure the volumes of the whole brain, contralesional brain (hemisphere), and residual brain regions of interest, and the

results indicated increased brain volume after the intravenous MSC infusions. The histological analyses revealed increased thicknesses of the contralesional cortex and corpus callosum in the MSC group compared with those in the vehicle group ($p = 0.021$, $p = 0.019$), which confirmed the volume increases. In the contralesional cortex, the MSC-treated group exhibited significant increases in the numbers of NeuN-positive cells ($p = 0.004$) and synaptic puncta ($p = 0.000$) compared with those in the vehicle group.
Conclusions: The intravenous infusion of MSCs resulted in improvements in functional outcome, increased brain volume, and enhanced synaptogenesis in HI rats.

Disclosures: T. Sakai: None. **M. Sasaki:** None. **Y. Kataoka-Sasaki:** None. **S. Oka:** None. **M. Nakazaki:** None. **S. Fukumura:** None. **M. kobayashi:** None. **H. Tsutsumi:** None. **J.D. Kocsis:** None. **O. Honmou:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.06/B22

Topic: A.04. Transplantation and Regeneration

Support: CSUN Thesis Project Grant

Title: Human neural progenitor cells reverse symptoms and extend longevity in a rat model of ataxia

Authors: *W. M. TIERNEY[1], B. ORTEGA[1], A. LEMUS[1], T. L. UHLENDORF[1], J. OCHOA[2], W. VAN TRIGT[2], A. KOPYOV[2], O. V. KOPYOV[2], R. W. COHEN[1]
[1]California State University, Northridge, Northridge, CA; [2]Celavie Biosciences, LLC, Oxnard, CA

Abstract: The spastic Han Wistar (sHW) rat serves as our model for human ataxia presenting symptoms of motor deterioration, decreased weight and a shortened lifespan. Correspondingly, sHW rats show progressive loss of Purkinje cells starting at 30 days. Past experiments in our lab revealed that human neural progenitor cells (NPCs) have been effective in this ataxic rat model, including significant improvements in behavioral assays and human cell survival 20 days post-transplantation. Here, we examined the longer-term effectiveness and fate of human NPCs in this ataxic rat. For this experiment, rats were placed into four treatment groups (equal mix of male and female rats): an untreated normal control group (n=10), an untreated mutant rat control (n=10), a mutant group that received an injection of dead NPCs (n=9), and a mutant group that received live NPCs (n=10). Bilateral cerebellar injections of 500,000 of either live or dead NPCs were performed on mutant sHW rats at 40 days of age, and motor activity (via open field and rotarod assays) was tested twice per week henceforth. All mutant rats started to decline in open

field testing around day 35. However, at day 45, the live NPC-treated mutants began to exhibit improved motor activity while dead NPC-treated and untreated mutants continued to display decreased motor abilities. Starting at day 60 (20 days post-transplantation), live NPC-treated mutant's motor behavior was statistically similar to normal rats, and this trend continued until the end of the experiment. Cerebellar decline was tested via the rotarod test. Live NPC mutants were statistically similar to normal rats; yet, dead NPC and untreated mutants showed significant decreases in rotarod performance. All rats were perfused with 4% paraformaldehyde, their brains removed and sliced for histological staining. While immunohistochemistry revealed few surviving human NPCs in the cerebellums of 100 day old NPC-treated mutants, cresyl violet staining revealed that live NPC-treated mutants had significantly more surviving Purkinje neurons as compared to mutants that were untreated or received dead NPCs. Implantation of live NPCs alleviated the symptoms of ataxia, acting as a neuroprotectant for the remaining Purkinje neurons, but paradoxically did not survive 60 days post-transplantation.

Disclosures: W.M. Tierney: None. **B. Ortega:** None. **A. Lemus:** None. **T.L. Uhlendorf:** None. **J. Ochoa:** None. **W. van Trigt:** None. **A. Kopyov:** None. **O.V. Kopyov:** None. **R.W. Cohen:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.07/B23

Topic: A.04. Transplantation and Regeneration

Support: CIHR Grant 480237
CIHR Grant 499146

Title: Transplanting immortal orexin neurons in narcolepsy

Authors: *S. K. PINTWALA[1], J. CHALMERS[2], J. FRAIGNE[1], D. BELSHAM[2], J. PEEVER[1]
[1]Cell and Systems Biol., [2]Physiol., Univ. of Toronto, Toronto, ON, Canada

Abstract: Narcolepsy is a sleep disorder caused by loss of orexin neurons in the lateral hypothalamus. This results in symptoms such as excessive daytime sleepiness and cataplexy, a sudden and involuntary loss of muscle tone during wake. The objective of cell transplantation is to treat disease by reinstating lost transmission, but is dependent on the availability of cells with phenotype of those lost. The aim of this study is to investigate the physiology of a novel, immortal orexin cell line and to perform cell transplants using a mouse model of narcolepsy. To do this, we used an immortal cell line isolated from transgenic mice (m) expressing green fluorescent protein (GFP) in orexin (ORX) neurons, isolated from the adult (A) hypothalamus (Hypo)—the mHypoA-ORX/GFP4 cell line. First, we performed immunocytochemistry against

GFP, the fluorescent marker which denotes these cells, and orexin-A to confirm the phenotype. Next, we performed a live cell secretion assay, coupled with enzyme immunoassay, to confirm the ability of these cells to secrete orexin. Finally, we performed transplant surgeries in a mouse model of narcolepsy (orexin-knockout) to determine cell survival. Cells were bilaterally injected into the prefrontal cortex (AP: 1.8/ ML: 0.4/ DV: 1.5, approx. 2000 cells/hemisphere). Cells were visualized using immunohistochemistry.
All (100%) of neurons in the mHypoA/ORX-GFP4 (#cells=379; n=3) cell line expressed orexin-A and GFP antigens. Using a live cell assay we detected orexin-A secretion at baseline (0.276±0.030ng/ml; n=3; 5.0mM glucose media). To probe orexin-A release, cells were challenged with a hypoglycemic condition (0.2mM glucose media) and found a significant increase in orexin-A release (0.337±0.031ng/ml; t-test; n=3; $p<0.01$). Finally, cells were transplanted to the brains of narcoleptic mice. GFP+ cells were found at 2 (#cells=731±382; n=4), 14 (#cells=1186±603; n=6) and 30 days (# cells=963±192; n=6) post-transplant.
This experiment highlights the potential of cell replacement therapy as a novel therapeutic strategy for narcolepsy, and the potential for using immortal cells to accomplish this.

Disclosures: S.K. Pintwala: None. **J. Chalmers:** None. **J. Fraigne:** None. **D. Belsham:** None. **J. Peever:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.08/B24

Topic: A.04. Transplantation and Regeneration

Support: NIH NINDS R21, NS088943
NIH NIMH R01, MH070596
NYSTEM IDEA

Title: Neovascularization for optimal survival of neural transplants

Authors: *J. E. KRZYSPIAK[1], B. GALINSKI[1], P. J. LITUMA[1], J. YAN[1], S. G. KEE[2], S. ZUKIN[1], D. WEISER[1], P. CASTILLO[1], K. KHODAKHAH[3], J. M. HEBERT[1]
[2]Dominick P. Purpura Dept. of Neurosci., [1]Albert Einstein Col. of Med., Bronx, NY; [3]Dept Neurosci., Albert Einstein Col. Med., Bronx, NY

Abstract: The transplantation of neural stem cells holds great promise for improving function after various forms of brain damage and disease. Days or weeks after transplantation, however, transplant-derived cells can be greatly reduced in numbers. The loss of transplanted cells has been attributed in part to immunorejection. However, there is growing evidence in the field that supporting cell types may be required to facilitate the success of a transplant in contrast to

transplanting pure populations of cells. Specifically, there is evidence that neovascularization may also be critical for transplant cell survival. As in the fetus where vascularization must match the physiological demands of each growing tissue, vascularization of neural cell transplants might also need to occur rapidly to promote optimal neuron survival, differentiation, and function. Our preliminary studies with transplants of cortical precursorsembryonic forebrain cells into the adult neocortex of a stroke affected mouse suggest that vascular endothelial precursors may be required in the transplant cell population for efficient survival of the neural precursors and the neurons they generate. We observe that within transplants on the stroke affected side, blood vessels primarily develop from donor-derived cells, in contrast to the control side, and appear to fuse with the host vasculature. Moreover, our early findings suggest that other cell types, such as microglia, might play critical roles in transplant neovascularization.
To show that donor-derived vessels are integrating with the host circulation, we are using an intravenous fluorescent dye to confirm bona fide fusion with host vessels. To determine the requirement of vascular precursor cells for enhanced cell survival, we are currently experimenting with two mixes of cell types for transplantation: one that contains the complete heterogeneous population of cells harvested from mouse embryonic cortices and one that lacks specifically the vascular precursor cells. To show that donor-derived vessels are integrating with the host circulation, we are using an intravenous fluorescent dye to confirm bona fide fusion with host vessels.Future studies will be using human embryonic stem cell derived neural stem cells and human umbilical cord derived endothelial cells to test if this phenomenon to is applicable to cultured human cells. These studies are directly relevant to the effective use of neural cell transplants in future clinical trials.

Disclosures: J.E. Krzyspiak: None. **B. Galinski:** None. **P.J. Lituma:** None. **J. Yan:** None. **S.G. Kee:** None. **S. Zukin:** None. **D. Weiser:** None. **P. Castillo:** None. **K. Khodakhah:** None. **J.M. Hebert:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.09/B25

Topic: A.04. Transplantation and Regeneration

Support: NIH-R01-AG048099
NIH-R01-AG056303
NIH-R01-AG055524
NIH-P50-AG01657
CIRM RT3-07893
Alz. Assoc. BFG-14-317000

Title: Development of murine/human microglia chimeras to study neurological disease

Authors: *M. A. COBURN, J. HASSELMANN, D. X. FIGUEROA, A. MCQUADE, C. H. TU, J.-P. CHADAREVIAN, H. DAVTYAN, S. GANDHI, M. BLURTON-JONES
Neurobio. and Behavior, Univ. of California, Irvine, Irvine, CA

Abstract: Microglia are strongly implicated in the pathogenesis of Alzheimer's Disease (AD) and recent GWAS studies have identified several microglia-enriched genes that influence AD risk. Yet the impact of these genetic variants on microglial function remains unclear. Our lab recently developed a fully-defined approach to differentiate induced pluripotent stem cells (iPSCs) into microglia (iMGLs), providing an important tool to study human microglia *in vitro*. However, microglial function is dramatically influenced by other cell types and pathologies within the brain, underscoring the need to also examine human microglial function *in vivo*. Lineage tracing studies reveal that microglia originate from primitive hematopoietic progenitors (HPCs) within the yolk-sac that migrate into the developing brain. We therefore reasoned that transplantation of HPCs into postnatal immune-deficient mice with humanized CSF-1 would allow us to recapitulate this developmental program and generate murine/human microglia chimeras. Transplanted HPCs readily differentiated into human microglia, exhibiting typical microglial markers and morphology. In addition, HPCs also differentiated into three other CNS macrophages (perivascular, meningeal, and choroid plexus macrophages), all of which can be derived from yolk sac HPCs. Our protocol thereby reproduces microglial ontogeny, allowing transplanted HPCs to proliferate and differentiate appropriately in response to extrinsic cures within the developing rodent brain. To further establish the utility of this approach we have performed experiments to examine the impact of systemically induced neuroinflammation though lipopolysaccharide (LPS) stimulation on human microglial morphology and gene expression, validated through histology, two-photon live imaging, and RNA sequencing. Additionally, analysis of focal laser damage under a two-photon microscope allows us to assess the effect of localized damage response and infiltration of transplanted microglia. Together our data suggests that this approach can be used to produce a novel and informative humanized mouse model of neuroinflammation.

Disclosures: M.A. Coburn: None. **J. Hasselmann:** None. **D.X. Figueroa:** None. **A. McQuade:** None. **C.H. Tu:** None. **J. Chadarevian:** None. **H. Davtyan:** None. **S. Gandhi:** None. **M. Blurton-Jones:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.10/B26

Topic: A.04. Transplantation and Regeneration

Support: NMRPD1E1393
NRRPD1G0111
CMRPG3C1543
CMRPG5C0073

Title: Psychophysical assessment of tactile sensory functions in microsurgical rat models

Authors: *S.-H. WU[1,4], C.-J. WEN[1,4], J.-J. HUANG[5,4,1], Y.-C. PEI[5,1,4], C.-H. LIN[1,4,2,3], H.-Y. CHENG[1], Z.-L. PENG[1,2,3], H.-Y. YANG[6], F.-C. WEI[1,4,3]
[1]Ctr. for Vascularized Composite Allotransplantation, [2]Div. of Trauma and Emergency Plastic Surgery, [3]Div. of Plastic Reconstructive Microsurgery, Linkou Chang Gung Mem. Hosp., Taoyuan City, Taiwan; [4]Col. of Med., Chang Gung Univ., Taoyuan City, Taiwan; [5]Dept. of Physical Med. and Rehabil., Taoyuan Chang Gung Mem. Hosp., Taoyuan City, Taiwan; [6]Dept. of Electronic Engin., Natl. Taipei Univ. of Technol., Taipei City, Taiwan

Abstract: Vascularized composite allotransplantation (VCA) is a powerful tool for human body reconstruction, which allows severe limb and facial defects to be reconstructed by genetically non-identical tissues. The functional outcome is one of major concerns for VCA. However, the lack of the rigorous method for quantifying the postoperative function makes the assessment of the long-term recovery difficult. Therefore, developing an appropriate animal model, which can systematically assess the functional recovery, will help scientists discover more potential treatments to improve the nerve reinnevation in VCA. The mystacial pad flap, also known as the whisker system, is a suitable animal model for VCA studies because its function is easily to be monitored by the whisking-related behavior. Here we designed a two-alternative forced-choice tactile discrimination task to evaluate the whisker sensory function in *Lewis* rats. In this task, the rat had to use its whisker to discriminate the target texture from two tactile stimuli presented simultaneously to get the reward (6% sucrose solution). The proportion of correct decision (Pc) would be calculated after 60 sequential trials in one session, and each rat would repeatedly perform 4-5 sessions in each week. Our rats were able to acquire the skill, i.e. the proportion of correct decision greater than 75%, within 1.5 months. Next, we manipulated the infraorbital nerve, which is responsible for tactile sensation in the mystacial pad flap, on the well-trained rats by microsurgical technique. We found that rats' Pc sharply dropped down to the chance level (50%) after we cut off their infraorbital nerve, but the decrease of the Pc did not occur in the subjects who received the sham surgery. Furthermore, we cut the infraorbital nerve first and then sutured it back. Rats' Pc also had dropped down in the first postoperative week, but it gradually recovered to the baseline around the second to third postoperative week. This result suggests that our tactile discrimination task is able to quantify the whisker sensory function after the surgical operation. Compared with the traditional behavior paradigms, such as the pain or thermal test, our psychophysical task provides a more reliable and repeatable way for long-term monitoring. In addition, the action of rats' active discrimination is similar to rehabilitation, so this paradigm has the potential to serve as the animal model for rehabilitation. Our future work will focus on VCA rat models, and try to combine this behavior task with the brain image technique to study the mechanism of the nerve reinnvervation after VCA.

Disclosures: S. Wu: None. **C. Wen:** None. **J. Huang:** None. **Y. Pei:** None. **C. Lin:** None. **H. Cheng:** None. **Z. Peng:** None. **H. Yang:** None. **F. Wei:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.11/B27

Topic: A.04. Transplantation and Regeneration

Support: VA-CDA

Title: Optimizing the survival of transplanted engineered neural tissue grafts using necrostatin-1 and methylprednisolone

Authors: *G. MAN[1], D. JGAMADZE[1], B. GU[1], J. LIM[1], V. LIAUDANSKAYA[2], D. L. KAPLAN[2], H.-C. I. CHEN[1]
[1]Neurosurg., Univ. of Pennsylvania, Philadelphia, PA; [2]Biomed. Engin., Tufts Univ., Medford, MA

Abstract: Introduction: Transplantation of three-dimensional neural tissue constructs emulating features of native neural tissue could effectively replace large brain defects and restore circuit function. An obstacle to this strategy is cell death after transplantation, especially in the context of acute injury or ischemia. In a rat model of motor cortex aspiration injury, we assessed the effect of inhibiting necroptosis and inflammation on the survival of human cortical neurons derived from induced pluripotent stem cells (iPSC) seeded on a silk sponge scaffold. Methods: Human cortical neurons were differentiated from iPSC lines. The phenotype of these neurons was characterized over the course of 80 days by standard immunocytochemistry. Neurons differentiated from GFP+ iPSC lines (day 30) were seeded on a silk sponge scaffold and embedded in a fibrin hydrogel with and without necrostatin-1, a necroptosis inhibitor, and methylprednisolone (MP), a corticosteroid. These silk constructs were transplanted into the primary motor cortex of adult male Sprague-Dawley rats after an aspiration lesion had been created. Three days after surgery, the animals were sacrificed, the brains extracted for immunohistochemistry. Results: iPSC-derived cells seeded on silk scaffolds consisted of a mixture of neurons (68% βIII-tubulin+) and neural progenitors (43% Pax6+). Most cells expressed the forebrain marker Foxg1 (72%). Animals were transplanted with silk constructs containing necrostatin-1 and MP (n=3) or with silk constructs lacking these agents (n=3). Qualitatively, there was considerably more survival in the former group compared to the latter group. Preliminary quantification of GFP+ area as a percentage of injury cavity size supported this qualitative finding (0.51 ± 0.18 versus 0.27 ± 0.06, $p=0.02$). The majority of the GFP+ cells within the graft were Tuj1+, indicating a neuronal phenotype. Initial quantification of CD68+ inflammatory cells per injury area suggested no difference between the two groups ($p=0.35$).

Conclusion: We have demonstrated that the local presence of a necroptosis inhibitor and corticosteroid improves the survival of transplanted 3D constructs consisting of iPS-derived human cortical neurons seeded on a silk scaffold. Ongoing studies are evaluating graft survival at later time points and more thoroughly examining the inflammatory response. These results indicate that pharmacological interventions can have a significant impact on the survival of transplanted neurons, which could greatly facilitate studies of the anatomical and functional integration of engineered neural tissues with the brain.

Disclosures: G. Man: None. **D. Jgamadze:** None. **B. Gu:** None. **J. Lim:** None. **V. Liaudanskaya:** None. **D.L. Kaplan:** None. **H.I. Chen:** None.

Poster

638. Transplantation and Regeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 638.12/B28

Topic: A.04. Transplantation and Regeneration

Title: Development of biomaterial-based cell transplantation strategies using zebrafish as an *in vivo* system

Authors: *B. B. PATEL[1], E. M. KOZIK[1], J. A. KUHLMAN[1], M. MCNAMARA[2], N. N. HASHEMI[2], D. S. SAKAGUCHI[1]
[1]Genetics, Develop. and Cell Biol., [2]Mechanical Engin., Iowa State Univ., Ames, IA

Abstract: The damaged mammalian central nervous system (CNS) has a limited ability to regenerate making the treatment of CNS injury and diseases difficult. Cell transplantation strategies are currently under extensive investigation as a potential approach for CNS repair. However, transplanted cells often have a low survival rate and poor host integration. To overcome these limitations, biocompatible materials can provide structural support and physical cues to direct cell growth and differentiation. In the present study, we aim to use zebrafish as an *in vivo* model system to study biomaterial-based cell delivery systems. Zebrafish provide an ideal vertebrate model as they have an innate immune system that is similar to mammals, develop *ex utero,* and are optically transparentas larvae, enabling implant and transplantation studies to be followed *in vivo*. To test whether biocompatible materials can improve cell viability and integration, *Xenopus* retinal glial (XR1) cells were labeled with fluorescent dyes to distinguish them from host tissues, and seeded onto polymer scaffolds. Unlike mammalian cells, *Xenopus* and zebrafish-derived cell lines have the advantage of being cultured at room temperature, supporting cell survival in a zebrafish. GFAP:GFP transgenic zebrafish larvae were used to follow the host glial response to the XR1-polymer implants. Implants were performed into the brain and eye of the zebrafish and the CNS microenvironment was examined by monitoring changes in brain morphology post implantation. Further, the larvae were time lapse-imaged

overnight, whole-mount imaged and sectioned post implantation to further characterize the glial response. Our results demonstrate that *in vitro*, XR1 cells attach and proliferate on the scaffolds. Secondly, scaffolds were successfully implanted into zebrafish, and that at least 4 days post implant the scaffolds are retained. This approach may provide a means for rapid screening of biocompatible materials in support of cell transplantation for *in vivo* delivery for CNS repair following injury.

Disclosures: B.B. Patel: None. **E.M. Kozik:** None. **J.A. Kuhlman:** None. **M. McNamara:** None. **N.N. Hashemi:** None. **D.S. Sakaguchi:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.01/B29

Topic: A.07. Developmental Disorders

Support: Virginia G. Piper Charitable Trust
The Helios Education Foundation at the Translational Genomics Research Institute

Title: Protecting dna: Shortened telomere length is associated with autism spectrum disorder but is not related to symptoms or cognition

Authors: *B. B. BRADEN[1], C. R. LEWIS[2], N. WALKER[2], F. TAGUINOD[2], K. AGRAWAL[2], W. JEPSEN[2], M. J. HUENTELMAN[2], C. J. SMITH[3], S. RINGENBACH[4]
[1]Dept. of Speech and Hearing Sci., Arizona State Univ. - Tempe Campus, Tempe, AZ; [2]Neurogenomics, Tranlsational Genomics Res. Inst., Phoenix, AZ; [3]Southwest Autism Res. and Resource Ctr., Phoenix, AZ; [4]Hlth. Solutions, Arizona State Univ., Tempe, AZ

Abstract: The diagnostic criteria for Autism Spectrum Disorder (ASD) includes two domains: social communication impairments and restricted, repetitive behaviors and interests. However, individuals with ASD commonly experience cognitive deficits. One possible mechanism of cognitive deficits in ASD is the shortening of telomeres. Telomeres are repetitive non-coding DNA nucleotides that protect genes by capping chromosome ends. Recently, two reports introduced preliminary evidence associating shortened telomere length with ASD or familial relation. Further, shortened telomeres have been associated with age-related cognitive decline. While it has been demonstrated that telomere length is not related to core symptoms of ASD, the relationship between telomere length and cognitive function in ASD has not been investigated. Using blood leukocyte-derived DNA, we investigated the association between relative telomere length (RTL) and ASD in males (ASD [mean age: 8.7±8.4], n = 116; typically developing [TD, mean age: 7.1±2.3], n = 71). We used an established quantitative polymerase chain reaction method, and designed telomere and single-copy reference gene primers as controls. We assessed

RTL between groups using ANCOVA with age as a covariate. Additionally, we hypothesized that shorter telomere length would be associated with lower levels of cognitive function as measured by the Stanford-Binet Intelligence Scale-5, but not core symptoms (i.e. Autism Diagnostic Observation Schedule and Social Responsiveness Scale) or sensory symptoms (i.e. Sensory Profile). We replicated previous findings that individuals with ASD have shortened RTL, compared to TD individuals ($p<0.001$). There were no significant associations between shortened telomere length and level of cognitive functioning, core ASD symptoms, or sensory symptoms. Taken together, these evidence strongly suggest that telomere length is affected in individuals with ASD, but the behavioral consequences remain unknown.

Disclosures: B.B. Braden: None. **C.R. Lewis:** None. **N. Walker:** None. **F. Taguinod:** None. **K. Agrawal:** None. **W. Jepsen:** None. **M.J. Huentelman:** None. **C.J. Smith:** None. **S. Ringenbach:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.02/B30

Topic: A.07. Developmental Disorders

Support: International Rett Syndrome Foundation (IRSF grant#3212)
Ontario Rett Syndrome Foundation (ORSA)

Title: Investigating the DNA methylation signature of the brain in Rett syndrome patients

Authors: *M. RASTEGAR[1], D. KROFT[2], K. SHEIKHOLESLAMI[4], S. AMIRI[2], V. SIU[5], T. PEMBERTON[2], M. DEL BIGIO[3]
[1]Dept. of Biochem. and Med. Genet., [2]Biochem. and Med. Genet., [3]Pathology, Univ. of Manitoba, Winnipeg, MB, Canada; [4]Med., Univ. of Toronto, Toronto, ON, Canada; [5]Biochem., Western Univ., London, ON, Canada

Abstract: Rett Syndrome (RTT) is an X-linked progressive neurodevelopmental disorder that is caused by *MECP2* gene mutations. RTT is one of the leading causes of mental disability in young females and has no cure or effective treatment. Individuals with RTT develop normally during their first 6-18 months of life, but then start to exhibit symptoms that include developmental regression, mental disability, seizers, speech problems, anxiety, and autistic characteristics. We have previously shown the expression of MeCP2 isoforms E1 and E2 to vary temporally and regionally during brain development and in the adult mouse brain. Moreover, we found that MeCP2E1 and E2 are differentially controlled by DNA methylation and that specific types of DNA methylation regulate MeCP2 homeostasis. Thus, genome-wide patterns in DNA methylation might be perturbed to varying extents in different regions of RTT brains. Here, we

explore genome-wide DNA methylation patterns in human post-mortem RTT brains using genomic DNA extracted from the cortex, hippocampus, amygdala, and cerebellum of RTT patients with confirmed *MECP2* gene mutations and age-/sex-matched controls. Global DNA methylation patterns were determined using Illumina's Infinium MethylationEPIC BeadChip, while global levels of different types of DNA methylation were studied by dot blot analysis. Comparative analyses of global 5mC and 5hmC as well as MethylationEPIC data in RTT patients and controls identified clear differences in the methylation patterns of specific gene promoter regions across different brain regions. Additional permutation-based significance tests identified marginally significant ($p < 0.10$) differentially methylated regions between RTT patients and controls in cortex, amygdala, and cerebellum. Our results support existence of a distinctive DNA methylation signature in the human RTT brain, providing important new insights into how molecular abnormalities at the cellular levels may lead to compromised brain function in RTT patients.
Control brain tissues and some RTT brain regions were obtained through NIH NeuroBioBank Program (neurobiobank.nih.gov). Additional RTT brains were donated to the Rastegar lab by patient family members with proper consent for research. Research with human brain tissues was reviewed and approved by the University of Manitoba Bannatyne Campus research ethics board.

Disclosures: M. Rastegar: None. **D. Kroft:** None. **K. Sheikholeslami:** None. **S. Amiri:** None. **V. Siu:** None. **T. Pemberton:** None. **M. Del Bigio:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.03/B31

Topic: A.07. Developmental Disorders

Support: NIH Grant MH096093
NIGMS P50 GM085273
Harvey Family Endowment (ELB)

Title: Reducing noise in spit and brain: Multi-tissue deconvolution analysis reveals epigenetic differences in young children diagnosed with autism spectrum disorder

Authors: *B. S. MULLIGAN, J. M. STEPHEN[1], E. L. BEARER[2,3]
[1]Mind Res. Network, Albuquerque, NM; [2]Dept. of Pathology, UNM Sch. of Med., Albuquerque, NM; [3]Div. of Biol., Caltech, Pasadena, CA

Abstract: Autism Spectrum Disorder (ASD) refers to a range of mental conditions present from childhood characterized by difficulty with communicating, developing/utilizing social skills, and understanding abstract concepts. 1 in 59 Americans aged 8 have been diagnosed with ASD, with

presence in all demographics across ethnicity, sex, and socio-economic status. No cure nor unifying cause are known. Current diagnosis is behavioral assessment beginning at 18 months of age. A minority of children (42%) are diagnosed by 36 months, though it is known that early diagnosis is key to the effectiveness of interventions. In order to diagnose more quickly diverse groups of children, the biological mechanisms related to ASD must be discovered. We propose that a possible biological mechanism of ASD is global epigenetic change. We believe that changes in methylation impact the development of the neural system in a child with ASD that will be detectable across multiple tissues. To test this, children with ASD and non-ASD control children aged 1-4 were recruited for interviews and sample collection. From these children, 11 individuals' saliva (6 control and 5 ASD) were analyzed with Illumina HumanMethylation450 BeadChip. Control and ASD brain samples from a separate study were used for cross comparison. After initial processing yielded little variation between ASD and control global epigenetic patterns, saliva composition was found to be 62.42% (± 6.59 , SD) keratinocyte (K) in ASD saliva samples and 57.64% (± 9.14) K in control samples, with a total average composition of 59.48% (± 7.85) K. After correction, ASD-driven global variation was detectable across the saliva samples. Gene expression modified related to axonal guidance, neurogenesis, and similarly neural-focused functions. Similar corrections were made in the brain samples for relative contributions of neuronal versus glial cells, and then the saliva and brain sites were compared again, identifying sites and genes commonly altered in both brain and saliva. Methylation in the original cohort was confirmed by pyrosequencing and validated in a new cohort. These genes' role in neural development and maintenance provides targets for future exploration into a mechanism by which developing brains are or become autistic, and gives hope for earlier detection.

Disclosures: B.S. Mulligan: None. **J.M. Stephen:** None. **E.L. Bearer:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.04/B32

Topic: A.07. Developmental Disorders

Title: *In vivo* Perturb-Seq: Finding common ground for heterogeneous variants in autism spectrum disorder

Authors: *X. JIN[1], M. KO[1], S. SIMMONS[3], J. LEVIN[3], F. ZHANG[3], P. ARLOTTA[2]
[2]Stem Cell and Regenerative Biol., [1]Harvard Univ., Cambridge, MA; [3]Broad Inst., Cambridge, MA

Abstract: Autism Spectrum Disorder (ASD) comprises a broad collection of brain developmental and functional disorders with highly heterogeneous genetic contributions.

Hundreds of risk genes have been identified by whole exome sequencing of patients with ASD and intellectual disability. The rare de novo variants found in these genes have large effect sizes and are highly penetrant, but very little is known about how they contribute to ASD pathology. Challenges in the field remain: 1) systemic, causative genetic studies of hundreds of ASD risk genes are needed, but generating knockout mice for individual genes is time-consuming and costly; 2) although ASD appears to have a developmental origin, it is not known whether different risk variants affect shared brain cell types and/or developmental pathways.
I propose to develop tools to systematically study a subset of these de novo ASD risk genes, aiming to uncover shared cellular mechanisms that give rise to common ASD phenotypes. To achieve this, I will build on the Perturb-Seq platform, to use in vivo genome editing in rodent progenitor cells of the cortex in utero to generate mutations in ASD risk genes, and use high-throughput single-cell transcriptomics to find common cell types altered by these perturbations. Working with human geneticists, I will select a panel of ~40 ASD risk genes, and investigate their function with the Perturb-Seq platform. I expect to identify the neuronal and nonneuronal substrates altered by each of these ASD risk variants, and identify the developmental stages of their manifestation. By combining human genetics and neurobiology in a more scalable approach, I will be able to investigate many ASD risk genes in parallel to gain a broader understanding of how diverse genetic changes give rise to a shared pathology.

Disclosures: M. Ko: None. **S. Simmons:** None. **J. Levin:** None. **F. Zhang:** None. **P. Arlotta:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.05/DP01/C1

Topic: A.07. Developmental Disorders

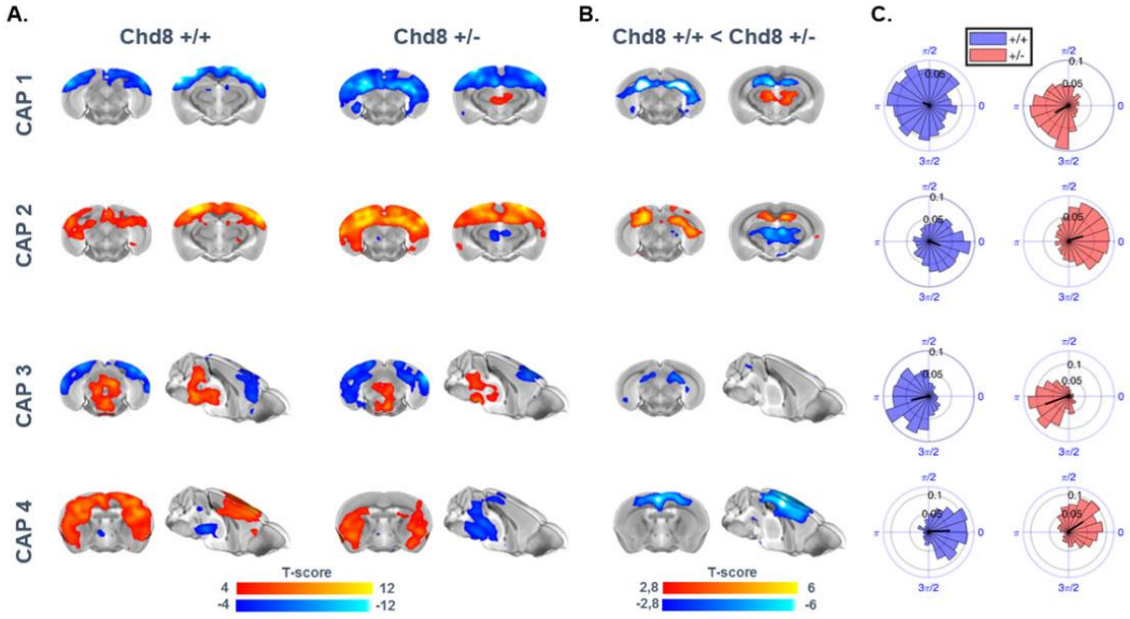
Support: SFARI #400101 to A.G.

Title: Altered brain-wide neural dynamics in mouse models of autism

Authors: D. GUTIERREZ-BARRAGAN[1], M. A. BASSON[2], S. PANZERI[1], *A. GOZZI[3]
[1]Inst. Italiano di Tecnologia, Rovereto, Italy; [2]King's Col. London, London, United Kingdom; [3]Fondazione Inst. Italiano Di Tecnologia, Genova, Italy

Abstract: Aberrant or disrupted brain functional connectivity is a hallmark feature of autism spectrum disorders (ASDs). When measured with neuroimaging techniques such as functional MRI in the resting state (rsfMRI), changes in interregional connectivity are typically mapped under the assumption that functional connectivity remains static over time. However, mounting experimental and theoretical work has implicated disrupted large-scale neural dynamics as a key

contributor to aberrant network activity. Here we applied a novel computational framework to probe the presence of altered neural dynamics in mouse lines harboring autism-associated mutations (*Chd8*$^{+/-}$, *Shank3B*$^{-/-}$ and *Cntnap2*$^{-/-}$) as measured with rsfMRI. By using a whole-brain clustering analysis of spontaneous rsfMRI activity, we could reliably classify, both at the group and single-subject level, a restricted set of brain-wide functional brain states, each characterized by a rich spatial structure that can be mapped with voxel-resolution. Importantly, we show that the dynamics of the rsfMRI states varies from state to state according to coupled oscillatory dynamics. Finally, we document that patterns of over- (*Chd8*$^{+/-}$) and under- (*Shank3B*$^{-/-}$, or *Cntnap2*$^{-/-}$) functional connectivity reflect the engagement of non-canonical brain states, characterized by regionally-altered patterns of spontaneous fMRI activity, as well as altered coupling among the oscillatory dynamics of each state. Collectively, our results offer a novel framework to interpret and model the emergence of aberrant functional connectivity in ASDs, and suggest that autism risk mutations lead to disrupted network activity via brain-wide alterations in spontaneous neural dynamics.



Disclosures: D. Gutierrez-Barragan: None. **M.A. Basson:** None. **S. Panzeri:** None. **A. Gozzi:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.06/C2

Topic: E.03. Basal Ganglia

Support: Department of Defense Grant W81XWH-15-1-0360

Title: Cell type-specific disruption of cortico-striatal circuitry drives repetitive and perseverative behaviors in fragile X syndrome model mice

Authors: *F. LONGO[1], S. ARYAL[1,2], J. TABOR[1], F. ALBANESE[1], J. D. ZHU[1], E. SANTINI[3], E. KLANN[1]
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]Dept. of Biochem. and Mol. Pharmacol., New York Univ. Sch. of Med., New York, NY; [3]Dept. of Neurol., Columbia Univ. Med. Ctr., New York, NY

Abstract: A significant proportion of individuals (15-50%) diagnosed with fragile X syndrome (FXS), the most common form of inherited intellectual disability, exhibit a variety of behaviors emblematic of autism spectrum disorders (ASD), including self-injury, stereotypy, and impaired social interaction (Penagarikano et al., 2007). These aberrations severely disrupt the health, safety, and quality of life of patients with FXS and ASD, and their families. Despite the clinical impact of these motor disturbances, relatively little is known about the underlying neurobiology of these features in comparison with other aspects of autism. Evidence from both clinical and preclinical studies suggests that the basal ganglia contribute to the pathophysiology of ASD (Hardan et al., 2003). It has been proposed that ASD symptoms such as cognitive inflexibility and impulsive/compulsive behavior might be generated by abnormalities in the striatum and in cortico-striatal circuits, as well as within striatal circuitry itself (Qiu et al., 2010). Consistent with this idea, FXS model mice display distinct repetitive/perseverative behaviors that are likely striatal-based, a brain area mostly unexplored in ASD. Altered protein synthesis may be a shared molecular anomaly that underlies the synaptic and behavioral impairments associated with ASD. Consistent with this hypothesis, a high proportion of patients with FXS, which is characterized by disrupted *de novo* protein synthesis, also suffer from autism. We hypothesized that the aberrant repetitive and perseverative behaviors exhibited by FXS individuals is due to a net increase in cap-dependent translation at cortico-striatal synapses and in particular in striatal medium spiny neurons (MSNs) and that alters the activity of direct and indirect pathways, causing changes in behavior. To dissect out the contribution of D1- versus D2- expressing MSNs in the dorsal striatum to repetitive and perseverative behaviors in FXS, we used a broad array of biochemical and genetic techniques and a newly developed RNA-sequencing technology, which allowed us to interrogate cell-type specific translatomes of the FXS mouse striatum at a genome-wide resolution. Our preliminary findings are consistent with the hypothesis that enhanced cap-dependent translation via increased eIF4E-eIF4G interactions contributes to repetitive behaviors displayed by FXS model mice that are likely cortico-striatal in nature and provide critical information concerning potential therapeutic treatments for synaptic and behavioral dysfunction not only FXS, but also in ASD.

Disclosures: F. Longo: None. **S. Aryal:** None. **J. Tabor:** None. **F. Albanese:** None. **J.D. Zhu:** None. **E. Santini:** None. **E. Klann:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.07/C3

Topic: E.03. Basal Ganglia

Support: NSF GRFP DGE-1656466
PNI Innovation Fund

Title: Perineuronal nets are increased on parvalbumin+ interneurons of the dorsomedial striatum in three mouse models of autism spectrum disorder

Authors: *B. A. BRIONES[1], M. N. PITCHER[2], A. D. ZYCH[2], A. E. HAYE[1], S. MURTHY[2], E. GOULD[1]
[1]Dept. of Psychology & Neurosci. Inst., [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder commonly associated with impaired social interactions and maladaptive repetitive behaviors, functions linked to the basal ganglia. Numerous studies have implicated basal ganglia and interneuron pathology in ASD, and furthermore that cortico-striatal dysfunction contributes to social impairment and repetitive self-injurious behaviors (Peca et al., 2011). In addition, a previous study reported that the disruption of fast-spiking parvalbumin (PV) + interneurons in the dorsal striatum of C57 mice produced impaired social interactions and stereotyped behavior (Rapanelli et al., 2017). In the striatum, PV+ interneurons receive direct pathway cortical and nigrostriatal input, project onto MSNs almost exclusively, and form synapses on their proximal dendrites. These findings might suggest that brain region-specific differences in interneuron plasticity contribute to the formation and learning of repetitive compulsive behaviors. Striatal PV+ interneurons are ensheathed by perineuronal nets (PNNs), extracellular matrix structures shown to be important for plasticity, and GWAS studies have shown abnormalities in extracellular matrix genes associated with ASD. No previous studies have investigated whether PNNs differ in the striatum of ASD mouse models compared to controls. To address this question, we stained for PV interneurons and PNNs with immunohistochemistry for PV and histochemistry for the PNN-binding lectin *Wisteria floribunda*, in the dorsomedial striatum (DMS) and dorsolateral striatum (DLS) of two genetic mouse models of ASD, Cntnap2$^{-/-}$ and Shank3ΔC$^{+/-}$, and one idiopathic model, BTBR compared to C57 controls. We found that a greater percentage of PV+ interneurons have PNNs in the DMS of all three mouse models of ASD compared to controls, this was not true for the DLS. We did not find any differences in dorsal striatum volume compared to controls, however the number of PV+ interneurons was

significantly decreased in the DMS of BTBR mice. These results suggest that enhanced PNNs in the DMS may reduce plasticity, thus increasing behavioral rigidity in ASD mouse models.

Disclosures: B.A. Briones: None. **M.N. Pitcher:** None. **A.D. Zych:** None. **A.E. Haye:** None. **S. Murthy:** None. **E. Gould:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.08/C4

Topic: A.07. Developmental Disorders

Support: NIH Grant MH101525
NSF Grant 1464686
W.M. Keck Foundation
NIH Grant EY026427
NIH Grant NS099709
NSF Grant 1707352

Title: Cortical hyperexcitation in early development results in autistic behavioral phenotypes

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

Abstract: Early development is marked by spontaneous neuronal activity that occurs without the input of sensory experience. This spontaneous activity has been demonstrated to refine foundational neural circuits before sensory input. By manipulating this activity in genetically-targeted pyramidal neurons within the cortex, we can interfere with the normal formation of specific neural circuits. Many psychiatric disorders are thought to be neurodevelopmental, stemming from malformation of neural circuits in early development. Autism disorders in particular have been associated with increased cortical excitation leading to a cortical imbalance of excitation to inhibition. Early disruptions to cortical activity may result in behavioral changes that correlate with psychiatric phenotypes typical of disorders such as autism.
Using optogenetics, we can manipulate neuronal activity using light. Due to the young age of the animals used in this study, a non-invasive light source must be used. Our laboratory has created mice that conditionally express a luciferase protein, sbGLuc, tethered to a channelrhodopsin, VChR1. This luminescent opsin, or luminopsin (LMO3), produces light, and thus a neuronal response, in the presence of the substrate coelenterazine (CTZ), which can be delivered intraperitoneally (IP). Lox-Stop-Lox LMO3 mice were crossed with Emx1-Cre transgenic mice, thus limiting expression of LMO3 to cortical pyramidal neurons. By delivering CTZ IP during

post-natal days 4-14, a hyperexcitation can be induced in the cortical pyramidal neurons of developing mouse pups. During adulthood, mice are tested behaviorally, and assessed for morphological and electrophysiological changes. Behavioral results indicate behavioral phenotypes consistent with autism behaviors. Electrophysiology indicates strongly increased excitation to inhibition and a lack of synchrony in the cortex. The results of this research will provide insight into the effect of altered developmental activity and its relationship to psychiatric disease.

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

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.09/C5

Topic: A.07. Developmental Disorders

Support: NSERC
Austism scholars
CIHR
CFREF

Title: Auditory processing deficits in Cntnap2-knock-out rats: Implications for neurodevelopmental disorders

Authors: *S. SCHMID[1], K. E. SCOTT[1], B. L. ALLMAN[2]
[2]Anat. and Cell Biol., [1]Univ. of Western Ontario, London, ON, Canada

Abstract: The mammalian auditory system undergoes considerable development and experience-dependent plasticity in early life. This normal maturation, however, is perturbed in individuals with neurodevelopmental disorders, such as autism spectrum disorder (ASD). These maturational differences may lead to impairments in auditory processing, and ultimately underlie the communication deficits and altered reactivity to sensory stimuli associated with ASD. For example, individuals with mutations in the autism-linked gene, contactin-associated protein-like 2 (CNTNAP2), experience language processing deficits, yet the contribution of CNTNAP2 to auditory function remains unknown. We addressed this question with a recently-developed rat model, using the neural measures of hearing sensitivity, auditory responsivity and speed of transmission, and behavioural measures of acoustic reactivity, sensory filtering and sensory-motor gating to allow a broad understanding of auditory system dysfunction across development and the behavioural consequences thereof. The auditory brainstem response (ABR), *in vivo* electrophysiological recordings from the primary auditory cortex, and manipulation of the acoustic startle response (ASR) were conducted in young (<P42) and adult (>P70) male and

female homozygous knockout (*Cntnap2*$^{-/-}$), heterozygous knockout (C*ntnap2*$^{+/-}$), and wildtype Sprague Dawley rats. Ultimately, we found the knockout rats to have typical hearing sensitivity but reduced neural responsivity in both the brainstem and cortex. Acoustic information was also transmitted slower throughout the brainstem auditory pathway in young *Cntnap2*$^{-/-}$ rats compared to age-matched wildtype controls; however, this *Cntnap2*-related delay was no longer present in adulthood. In contrast, the adult auditory cortex revealed a prolonged latency to the response onset and longer response duration. Behaviorally, while a short-term habituation deficit improved with age, the *Cntnap2*$^{-/-}$ rats displayed a heightened acoustic reactivity and sensory-motor gating deficit when young that worsened with age. To our knowledge, this study represents the first investigation into the role of *Cntnap2* in the development of auditory processing impairments which are found in individuals with neurodevelopmental disorders. Overall, these results provide insight into the altered maturation of the different levels of the auditory system and point to potential targets for intervention. Funding: NSERC, CIHR and Autism Scholars

Disclosures: S. Schmid: None. **K.E. Scott:** None. **B.L. Allman:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.10/C6

Topic: A.07. Developmental Disorders

Support: J.P. Bickell Foundation/ Medical Research Grant
CIHR Grant 388805
Scottish Rite Charitable Foundation of Canada Grant 17112

Title: Cerebrovascular deficits in a mouse model of the 16p11.2 deletion syndrome

Authors: *J. OUELLETTE[1,2], X. TOUSSAY[1], C. H. COMIN[4], M. HO[1], Y. TRUONG[3], C. MORSE[1], J.-F. THIBODEAU[5], M. YIN[6], M. LA CALLE[7], C. R. KENNEDY[5,2], D. BURGER[5,2], L. D. COSTA[4], D. J. STEWART[1], A. J. SHUHENDLER[3,8], B. LACOSTE[1,2,8]
[1]The Ottawa Hosp. Res. Inst., Ottawa, ON, Canada; [2]Cell. and Mol. Med., [3]Chem. and Biomolecular Sci., Univ. of Ottawa, Ottawa, ON, Canada; [4]IFSC, Univ. of Sao Paulo, Sao Paulo, Brazil; [5]The Ottawa Hosp. Res. Institute, Kidney Res. Ctr., Ottawa, ON, Canada; [6]FUJIFILM VisualSonics, Inc., Toronto, ON, Canada; [7]Montreal Neurolog. Institute, McGill Univ., Montreal, QC, Canada; [8]Univ. of Ottawa Brain and Mind Res. Inst., Ottawa, ON, Canada

Abstract: Brain development and function rely on vascular features that ensure adequate supply of oxygen and nutrients from the blood stream. These features consist of a well-established vascular network, a functional blood-brain barrier, as well as cerebral blood flow regulation.

Early life impairments in these features can lead to neurodevelopmental defects. Very few studies have considered the contribution of the brain vasculature to Autism Spectrum Disorders (ASD). A recent postmortem study suggested a possible impairment in angiogenesis (i.e. process through which new vessels are formed) in the young ASD brain. A possible link between ASD and altered cerebral perfusion has also been suggested. Yet, contribution of cerebrovascular deficits to ASD physiopathology remains elusive, and a detailed analysis of these deficits is needed. ASD are viewed as neurodevelopmental conditions associated with genetic origins. Mutations identified as a possible cause for ASD include the common 16p11.2 deletion, which leads to haploinsufficiency of 26 conserved genes. We are using a multidisciplinary approach in order to decipher the cerebrovascular underpinnings of ASD in a mouse model of the 16p11.2 deletion syndrome. We have identified functional and structural cerebrovascular deficits during postnatal development in constitutive 16p11.2+/- mutants. In particular, we evidenced in 16p11.2+/- mice a significant decrease in microvascular branching and density in the cerebral cortex at P14 ($p<0.01$; $n=12$), as well as a significant increase in microvascular branching and density at P50 ($p<0.05$; $n=12$) when compared to age-matched WT littermates. In addition, P50 16p11.2+/- mice display a collection of functional abnormalities when compared to WT mice, such as altered neurovascular coupling *in vivo* and altered vascular reactivity *ex vivo*. In particular, we demonstrate a defective endothelium-dependent vasodilation in 16p11.2+/- mice, while smooth muscle function is unaffected. Furthermore, we generated mice with endothelial-specific 16p11.2 haploinsufficiency (Ve-Cad-Cre;16p11.2flox/+) in order to dissect the endothelial contribution to ASD phenotypes. These mice underwent behavioral testing to assess whether they display ASD-related characteristics. We demonstrate that mice harboring the endothelial-specific 16p11.2 deletion show home cage hyperactivity, as well as motor coordination deficits in the rotarod test, both characteristics linked to the human 16p11.2 deletion syndrome. Altogether, our research program provides insight into how the vasculature controls critical features of brain development, and investigates ASD from a novel angle.

Disclosures: J. Ouellette: None. **X. Toussay:** None. **C.H. Comin:** None. **M. Ho:** None. **Y. Truong:** None. **C. Morse:** None. **J. Thibodeau:** None. **M. Yin:** None. **M. La Calle:** None. **C.R. Kennedy:** None. **D. Burger:** None. **L.D. Costa:** None. **D.J. Stewart:** None. **A.J. Shuhendler:** None. **B. Lacoste:** None.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.11/C7

Topic: A.07. Developmental Disorders

Title: Pro social effects of Oxytocin agonist in a PFC circuit model

Authors: *M. BENEKAREDDY[1], P. JANZ[2], C. GRUNDSCHOBER[3], F. KNOFLACH[4]
[1]Neuroscience, Ophthalmology & Rare Dis. (NORD) Translational Area, Roche Pharma Res. & Early Development, Roche I, Basel, Switzerland; [2]Fac. of Biol., Univ. of Freiburg, Freiburg, Germany; [3]Neurosci. Discovery and Biomarkers Roche Innovation Ctr. Basel, Roche Innovation Ctr., Basel, Switzerland; [4]Neurosci. Discovery and Biomarkers Roche Innovation Ctr. Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Abstract: Impaired social behavior is a major symptom in neurodevelopmental diseases such as autism spectrum disorders and schizophrenia. Previous studies show that the medial prefrontal cortex (PFC) is critically involved in governing social behavior (Yizhar et al., *Nature*, 2012; Benekareddy et al., *Biol Psychiatry*, 2017), and that acute hyperactivity in the PFC impairs social information processing and thereby social behavior. However, the cellular and circuit mechanisms that might be responsible for long-term social dysfunction remain poorly understood. We hypothesized that perturbing PFC circuit homeostasis over longer timescales would lead to social impairments in rats. DREADDs are ideally suited to ask this question as recent data has shown the effectiveness of clozapine-N-oxide (CNO) in activating DREADDs even after chronic application (Urban et al., 2016). To test the effect of chronic increase in PFC excitability on social behavior, we used AAVs to transduce CamKII-positive neurons with the activatory DREADD hM3D and treated the rats chronically with CNO before testing their social preference. Sociability was assessed in a 3-chamber task, following chronic CNO treatment. In a set of parallel experiments, acute PFC slices were prepared to perform electrophysiological recordings. Our data shows that chronic PFC hyperactivity leads to a persistent decrease in social interaction, associated with long-term PFC dysfunction. Field potential recordings in PFC slices revealed persistent alterations in synaptic transmission. Whole-cell patch clamp recordings from retrogradely-identified cortico-thalamic projection neurons demonstrated that the excitability of these neurons is altered. Further, to address the effect of Oxytocin agonist in this circuit model, we treated rats undergoing chronic PFC activation with the selective peptidic oxytocin agonist, RO6958375. Data from social behavior experiments and physiological characterization reveal an effect of RO6958375 in correcting the circuit and behavioral dysfunction caused by the disruption of the PFC network. Taken together this study highlights the role of the PFC network in dysfunctional social behavior and points to a circuit mode of action for the pro-social effects of oxytocin.

Disclosures: M. Benekareddy: A. Employment/Salary (full or part-time):; F. Hoffman-La Roche. **P. Janz:** None. **C. Grundschober:** A. Employment/Salary (full or part-time):; F. Hoffman-La Roche. **F. Knoflach:** A. Employment/Salary (full or part-time):; F. Hoffman-La Roche.

Poster

639. Genes and Molecules Implicated in Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 639.12/C8

Topic: A.07. Developmental Disorders

Support: Conacyt Scholarship No. 574809

Title: Effect of the environmental enrichment on the multiunitary activity of lobules VI & VII of the cerebellum in the autistic rat

Authors: *O. E. CRUZ MAGOS[1], J. A. PÉREZ RODRÍGUEZ[2], G. HERRERA MEZA[3], P. CARRILLO CASTILLA[4], P. PACHECO[5], L. I. GARCÍA[3], J. MANZO[6]
[1]Ctr. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa Enríquez, Mexico; [2]Ctr. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Veracruz, Mexico; [3]Ctr. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Mexico; [4]Inst. de neuroetología, Univ. Veracruzana, Xalapa, Ver, Mexico; [5]Inst. de Neuroetología, Univ. Veracruzana, Xalapa, Mexico; [6]Ctr. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Ver. Mexico, Mexico

Abstract: Autism is a neural developmental disorder that in children manifests itself as a spectrum of behavioral alterations between 2 and 3 years of age. Although the number of studies in this regard increases annually, significant physiological manifestations that allow to make laboratory diagnoses are still unknown. To date, autism continues to be diagnosed only on the basis of the subject's behavior. This is why it is relevant to find approaches that allow physiologicals determinations of the disorder. It is known that one of the structures invariably altered in autistic subjects is the cerebellum. Therefore, in this work we proposed the encephalographic record of this structure could serve as a basis for spectrum´s physiological analysis. To do this, a posnatal autistic model was used in Wistar rat by the posnatal injection of a daily dose of 150 mg / kg of valproic acid to pups from day P6 to P12. Four groups, Controls (Ct) in standard (SE) and enriched environment (EE), and Autistic (At) in SE and EE were used. All of them had a multi-unit registry of the cerebellar vermis, specifically lobes VI and VII . The results showed that EE impact on the amplitude response by different ways in all groups, but the At in SE presented a significant increase in the amplitude compared with Ct-SE, which was reduced when they were submitted to EE. Thus, we first observe that it is possible to identify encephalographic variations characteristic of autism in the cerebellum cortex, and that these increased variations can return to a level close to Ct after the subject is submitted to an environmental enrichment program. The significance of this amplitude in the discharge of the cerebellar cortex requires further studies. Conacyt Scholarship No. 574809 (OECM); Academic Body of Neurosciences (UV-CA-28).

Disclosures: O.E. Cruz Magos: None. **J.A. Pérez Rodríguez:** None. **G. Herrera Meza:** None. **P. Carrillo Castilla:** None. **P. Pacheco:** None. **L.I. García:** None. **J. Manzo:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.01/C9

Topic: A.07. Developmental Disorders

Support: NRF-2018M3C7A1024148
NRF-2018M3C7A1024150
NRF-2017R1A2B4012237

Title: Network based brain transcriptome analysis in Down syndrome

Authors: *S. SEOL[1], J. KWON[1], J.-S. HAN[2], H. KANG[1]
[1]Life Sci., Chung-Ang Univ., Seoul, Korea, Republic of; [2]Biol. Sci., Konkuk Univ., Seoul, Korea, Republic of

Abstract: Down syndrome (DS) (also known as Trisomy 21) is the most common genetic disorder causing intellectual disability. DS patients showed altered brain developmental characteristics that cause abnormal brain structure and function compared with normal subjects. To further investigate the underlying mechanisms of observed differences between DS and euploid controls at the system level, we performed weighted gene co-expression network analysis (WGCNA) using previously published transcriptome data set (GEO's GSE 59630). For analysis, we chose three regions, dorsolateral prefrontal cortex (DFC), cerebellar cortex (CBC) and primary visual cortex (V1C), which have the high coverages in developmental periods from mid-fetal to adult. The function of these three regions are also known to be related with Down syndrome phenotypes (cognition, motor coordination and vision, respectively). Principal component analysis showed that the samples from DS and controls are mainly clustered by more developmental stages and regions than disease status. From WGCNA, 49 modules were detected and the modules' eigengenes showed diverse correlation patterns with traits like developmental stages, regions and disease status of the samples. After defining modules, we conducted cell type enrichment analysis in each module using human and mouse brain RNA-seq database. Genes in some modules are enriched in distinct cell types and they also have unique gene expression patterns affected by regions, developmental stages, and disease status of the samples. We annotated these modules and analyzed Gene Ontology and KEGG pathways using DAVID. We built intramodular gene networks in each module and selected hub genes which have higher module membership. Through these analyses, we have created gene modules displaying unique gene expression patterns, and the annotations of these modules provide insights needed to discover relationship between genes and cell type-related phenotypes.

Disclosures: J. Kwon: None. **J. Han:** None. **H. Kang:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.02/C10

Topic: A.07. Developmental Disorders

Support: ALANA USA Foundation
Awakening Angels Foundation
Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq/MCTI)

Title: Characterization of early communicative behavior in mouse model of Down syndrome Ts65Dn and its response to pharmacological treatment using the NMDA-receptor antagonist memantine

Authors: *B. ZAMPIERI[1], M. W. JOHNSON[1], A. C. COSTA[2]
[1]Dept. of Pediatrics, [2]Departments of Pediatrics and Psychiatry, Case Western Reserve Univ., Cleveland, OH

Abstract: Down syndrome (DS) is the most prevalent chromosomal cause of intellectual disability. Language development is delayed in children with DS and many areas of speech are known to be impaired, yet the causal mechanisms of these deficits are not well understood. Isolation-induced ultrasonic vocalizations (USV) have been a commonly used behavioral measurement to assess developmental delays and communication deficits in mouse models of neurodevelopmental disorders. Here we investigated communication by means of isolation-induced pup USV from postnatal day (P) 3 to 21 in the Ts65Dn mouse model for DS. We also assessed the impact exerted on USVs emission by the inhibition of NMDA-receptor function with the antagonist memantine. In total, 36 untreated Ts65Dn, 22 treated Ts65Dn, 40 untreated euploid pups and 33 treated euploid pups were tested for USV recording. Memantine combined with NIH31 formula mouse diet (TestDiet, St. Louis, MO, USA) was administered orally at the doses of 200 mg/kg from P1 to P2, 500 mg/kg from P3 to P18 and 200 mg/kg from P19 to P21 of food for chronic memantine treatment. USVs were recorded every other day for 5 min inside a sound-attenuating chamber (SonoTrack SMART Chamber, Metris). Data were recorded at 250 kHz using a Sonotrack system (Metris). Acoustical analysis was performed using Avisoft Bioacoustics SasLab Pro software (Version 5.2.09) and IGOR Pro 6 (WaveMetrics). Spectrograms were generated with a Fast Fourier Transform (FFT)-length of 512 and a Flat top window with 87.5% overlap using Avisoft whistle detection algorithm and post-processed in IGOR Pro. Overall, we found differences between genotypes in both spectral and temporal properties of USVs emitted by untreated mice. In particular, Ts65Dn mice displayed a developmental delay in their emission rate of USVs with a peak in call number at P7 compared

to P5 for wild-type mice. A genotype-dependent difference was found in the total number of USVs when all ages were combined for the untreated groups (t test, $p < 0.0019$). Preliminary results show that the delay on the peak of USVs rate was not restored after administration of memantine. However, no difference in the total number of calls between untreated wild-type and treated Ts65Dn mice was observed. Memantine showed no or little effect on the qualitative parameters of USVs emitted by Ts65Dn pus mice. The impairment in ultrasonic communication during early development observed here is consistent with other behavioral phenotypes exhibited by Ts65Dn mice and mimics the atypical communication pattern observed in DS. The effect of memantine on the emission pattern of USV in Ts65Dn mice is being further investigated in our laboratory.

Disclosures: B. Zampieri: None. **M.W. Johnson:** None. **A.C. Costa:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.03/C11

Topic: A.07. Developmental Disorders

Support: Indiana Clinical and Translational Sciences Institute funded, in part by Grant Number UL1TR001108 from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award

Title: Characterization of developmental changes in Dyrk1a protein expression in the cortex, hippocampus and cerebellum in male and female Down syndrome mice

Authors: *L. E. HAWLEY[1], A. J. PARKER[1], M. E. STRINGER[2], C. R. GOODLETT[2], R. J. ROPER[1]
[1]Biol., [2]Psychology, IUPUI, Indianapolis, IN

Abstract: Down syndrome (DS) is caused by the triplication of human chromosome 21 (Hsa21) and is the leading genetic cause of intellectual disability. Dual-specificity tyrosine-phosphorylated regulated kinase 1A (DYRK1A), included on Hsa21, regulates several key pathways in cell proliferation and differentiation, and its triplication is thought to contribute to aberrant developmental process that lead to neurodevelopmental deficits, intellectual disability, and bone and craniofacial abnormalities. Limited information exists regarding regulation of DYRK1A expression across key periods of brain development and none exists concerning potential sex differences. Drug development efforts have used putative DYRK1A inhibitors in preclinical studies and in clinical trials to determine therapeutic potential to improve neurobehavioral phenotypes in individuals with DS. However, these studies are hampered by the lack of information about the expression and activity of DYRK1A protein during brain

development in mouse models of DS.
Ts65Dn is the most commonly used mouse model of DS and contains three copies of approximately half of the ~300 genes on Hsa21, including DYRK1A. We tested the hypothesis that expression of Dyrk1a from the late prenatal period through the first postnatal month of development in this DS mouse model will show temporal and spatial variation in the extent of overexpression in the developing brain, and that differences between the sexes may be apparent. Using Western blot analysis, Dyrk1a protein concentrations were quantified in the hippocampus, cerebral cortex, and cerebellum from embryonic day 18.5 to postnatal day 24 in euploid and trisomic male and female mice. Our data suggest that males and females have different patterns of Dyrk1a dysregulation, but also share some commonalities in time and brain region of Dyrk1a expression between euploid and trisomic mice. Identifying developmental periods of greatest elevation of Dyrk1a protein expression in specific brain regions, including the differences in temporal patterns between males and females, provides key information to inform new studies of mechanisms by which excessive Dyrk1a alters regional brain development and produces neurodevelopmental deficits characteristic of DS phenotypes.

Disclosures: L.E. Hawley: None. **A.J. Parker:** None. **M.E. Stringer:** None. **C.R. Goodlett:** None. **R.J. Roper:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.04/C12

Topic: A.07. Developmental Disorders

Support: ALANA USA Foundation
Technical support by Siemens Medical Solutions

Title: Young adults with Down syndrome show smaller hippocampal subfields measured with high-field MRI

Authors: *K. A. KOENIG[1], S.-H. OH[2], M. STASKO[3], E. LISSMORE[3], E. ROTH[3], A. BIRNBAUM[3], T. SCHEIDEMANTEL[4], H. TAYLOR[4], N. ROIZEN[4], S. RUEDRICH[4], A. C. COSTA[3]
[1]Cleveland Clin., Cleveland, OH; [2]Hankuk Univ. of Foreign Studies, Yongin, Korea, Republic of; [3]Case Western Reserve Univ., Cleveland, OH; [4]Univ. Hosp., Cleveland, OH

Abstract: Introduction: Down syndrome (DS) is the most common non-inherited genetic cause of developmental disability, leading to a range of well-described cognitive and physiological characteristics, including an increased incidence of dementia. Neuroanatomical features related to DS have been fairly consistently described, and generally include a decrease in the size of the

hippocampus. Here we report a comparison of hippocampal subfield volumes in young adults with DS and age-matched healthy controls. A more complete understanding of structural changes of the hippocampus has the potential to increase our understanding of the pathophysiology of DS. **Methods**: 13 young adults with DS (mean age 20.5 ± 5.6, 8 males) and 8 age-matched controls (mean age 20.6 ± 5.0, 4 males) were scanned in an IRB-approved protocol on a Siemens 7T Magnetom. Scans included a whole-brain anatomical MP2RAGE (0.75mm^3 isotropic voxel size) and a high-resolution GRE scan focusing on the hippocampus (0.375 x 1.0 x 0.375mm^3). Hippocampal subfield segmentation was performed using the Automated Segmentation of Hippocampal Subfields (ASHS) software and manually corrected if necessary. Subfield volumes were calculated and corrected for intracranial volume (ICV). Unpaired Student's t-tests with a correction for multiple comparisons were used to compare controls and those with DS. In participants with DS, subfield volumes were correlated with cognitive performance. **Results:** Groups did not differ in age ($p < 0.970$). ICV-corrected whole-brain grey and white matter volumes were smaller in those with DS ($p < 0.05$). Figure 1 shows a representative segmentation at the head of the hippocampus. Bilateral CA1, CA3, dentate gyrus, and total hippocampal volumes were smaller in those with DS (Table 1). Subfield volumes were not correlated with cognitive performance. **Discussion:** This work represents the first assessment of hippocampal subfield volume in DS at ultra-high field strength. We find that hippocampal subfield volumes are decreased bilaterally in those with DS, in agreement with reports of decreased myelin density.[1] A larger sample size may be needed to identify any relationship between cognitive performance and volume measures. 1. Ábrahám H. et al. *Int J Dev Neuroscience*. 2012; 30(2): 147-158.

Hippocampal subfield comparison between DS and controls

ROI	MEAN VOL	MEAN VOL	
LEFT	DS	CONTROL	p
entorhinal cortex	0.027	0.027	0.8794
subiculum	0.047	0.044	0.0685
CA1	**0.081**	**0.098**	**0.0004**
dentate gyrus	**0.042**	**0.053**	**0.0009**
CA3	**0.001**	**0.003**	**2.9×10^{-6}**
tail	0.008	0.010	0.0646
total	**0.180**	**0.209**	**0.0014**
RIGHT			
entorhinal cortex	0.030	0.026	0.2230
subiculum	0.040	0.037	0.1387
CA1	**0.100**	**0.111**	**0.0019**
dentate gyrus	**0.049**	**0.059**	**0.0026**
CA3	**0.000**	**0.001**	**0.0041**
tail	0.004	0.004	0.8192

total	**0.194**	**0.212**	**0.0046**
Comparisons in bold survived FDR correction.			

Disclosures: K.A. Koenig: None. **S. Oh:** None. **M. Stasko:** None. **E. Lissmore:** None. **E. Roth:** None. **A. Birnbaum:** None. **T. Scheidemantel:** None. **H. Taylor:** None. **N. Roizen:** None. **S. Ruedrich:** None. **A.C. Costa:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.05/C13

Topic: A.07. Developmental Disorders

Support: Linda Crnic Institute for Down Syndrome
Anna and John J. Sie Foundation

Title: Interferon signaling in Down syndrome

Authors: *K. SULLIVAN[1], K. SMITH[1], D. EVANS[1], H. LEWIS[1], A. PANDEY[1], A. HILL[1], A. RACHUBINSKI[1], K. WOLTER-WARMERDAM[2], F. HICKEY[2], T. BLUMENTHAL[1], J. M. ESPINOSA[1]
[1]Linda Crnic Inst. for Down Syndrome, Aurora, CO; [2]Children's Hosp. Colorado, Aurora, CO

Abstract: Trisomy 21 (T21) is the most common chromosomal abnormality in the human population, occurring in approximately 1 in 700 live births. The extra copy of chromosome 21 (chr21) impacts human development in myriad ways across every major organ system, causing the condition known as Down syndrome (DS). One of the most intriguing biomedical aspects of T21 is that it causes a novel disease spectrum in the DS population, protecting these individuals from some conditions (e.g. solid tumors), while strongly predisposing them to others (e.g. Alzheimer's disease, cognitive deficits, autoimmune disorders). In order to identify dysregulated molecular pathways that could contribute to the phenotypes associated with DS, we performed complementary transcriptome and proteome analysis from age- and sex-matched cohorts of individuals with T21 and euploid controls.
Transcriptome analysis revealed that T21 activates the interferon (IFN) transcriptional response in nine pairs of fibroblast and lymphoblastoid cell lines, and this observation was confirmed in freshly isolated circulating monocytes and T cells from 17 individuals, 10 with DS. The gene expression signature caused by T21 cells is dominated by induction of interferon-stimulated genes (ISGs) as well as decreased expression of ribosomal proteins and translation factors and is likely due to the fact that four of the six IFN receptors are located on chr21. Accordingly, T21 cells are hypersensitive to IFN ligands and show significant overexpression of ISGs in response

to IFN treatment. Furthermore, we show that pharmacological inhibition of JAK kinases, which function downstream of IFN receptors, reduces expression levels of ISGs and rescues growth defects in T21 cells.
Employing a cohort of 263 individuals, 165 with T21, we performed a plasma proteomics study that confirmed massive immune dysregulation in people with Down syndrome, including changes in many immune-modulatory factors that could be explained by chronic IFN hyperactivation. For example, levels of IL6, TNFα, MCP1, and IL22, are all increased in individuals with T21, while the levels of numerous components of the complement cascade are decreased.
These data are consistent with the observations that: 1) nearly 30% of individuals with T21 are affected by one or more autoimmune conditions and 2) brain tissue from people with T21 shows obvious signs of neuroinflammation across their lifespan, even in neonates. We hypothesize that chronic interferon activation is central to these autoimmune and autoinflammatory phenotypes, and that interferon antagonists may, therefore, have therapeutic benefits in DS.

Disclosures: K. Sullivan: None. **K. Smith:** None. **D. Evans:** None. **H. Lewis:** None. **A. Pandey:** None. **A. Hill:** None. **A. Rachubinski:** None. **K. Wolter-Warmerdam:** None. **F. Hickey:** None. **T. Blumenthal:** None. **J.M. Espinosa:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.06/C14

Topic: A.07. Developmental Disorders

Support: ALANA USA Foundation (Contracts 124124 and 200381)
Alana CWRU/MIT Collaborative Fund
The Hartwell Foundation Fellowship
Jerome Lejeune Foundation
Awakening Angels Foundation

Title: Quantitative analysis of retinal function during development by electroretinography in the Ts65Dn, a mouse model of Down syndrome

Authors: *J. J. SCOTT-MCKEAN[1], A. C. S. COSTA[1,2]
[1]Dept. of Pediatrics, [2]Dept. of Psychiatry, Case Western Reserve Univ., Cleveland, OH

Abstract: Down syndrome (DS) results from an extra copy of chromosome 21 (trisomy 21) and is the most common genetically defined cause of intellectual disability. There are an estimated 83,000 children, out of an overall population of over 300,000 individuals, living with DS in the US. Visual system deficits have been associated with DS, affecting academic performance in

school age children, which can negatively impact their cognitive development and daily life. The electroretinogram (ERG) provides information about the electrical activity of various retinal cell populations in response to light stimuli, and is a useful tool for assessing various retinal diseases, including retinal degeneration. In this study, we utilized the Ts65Dn mouse model of DS, which mimics many phenotypes seen in persons with DS, including impaired visual function. Flash, full-field (Ganzfeld) ERGs were used to track basic retinal function in Ts65Dn mice at three different stages of development (young (17 day old), early adult (35 day old), and mature adult (3-5 month old)). Mice were anesthetized with 20% urethane (8.0 ml/kg, intraperitoneally (i.p.)). A Ganzfeld ERG system was used to evoke and record flash ERGs using the following protocol (green light: 504nm; flash duration: 1 ms; interstimulus intervals of 0.7 s for stimulus intensities -4.7 to -2.0 log (cd s/m^2) and 10 s for stimulus intensities -1.7 to 2.2 log (cd s/m^2); and an average of 5-20 flashes per recording). We found that adult Ts65Dn mice displayed abnormal ERGs when compared to euploid littermate control mice. Specifically, under urethane anesthesia, these mice exhibit deficits in A-wave amplitude, and larger maximum oscillatory potentials (OPs), when compared to control mice. However, there was no difference in B-wave amplitude in Ts65Dn mice when compared to control mice. We than assessed whether memantine could rescue retinal function differences in Ts65Dn mice. Memantine (5 mg/kg, i.p.) was injected 15 min prior to the start of ERG recordings, and all experiments lasted no longer than 20 min. In adult Ts65Dn mice, memantine significantly increased A-wave amplitudes to levels similar to those seen in control mice. However, memantine did not decrease OP amplitudes in Ts65Dn mice. Together, these results show that retinal activity is abnormal in Ts65Dn mice, and memantine can at least partially rescue retinal function. The data presented here provides a basic information about the development of retinal function in the Ts65Dn mouse, which may lead to a better understanding of sensory deficits in children with DS and guide the development of pharmacotherapies aimed at improving the quality of life of this vulnerable population.

Disclosures: J.J. Scott-McKean: None. **A.C.S. Costa:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.07/C15

Topic: A.07. Developmental Disorders

Support: ANR-10-IAIHU-06
Fondation Jérôme Lejeune
Fondazione Generali e Assicurazione Generali
Fondazione de Monte

Title: Neurogenesis deficits in Down syndrome: Testing recovery with GABAα5 negative allosteric modulator, β2 adrenergic agonist and IGF-1 in Ts65Dn mice

Authors: *M.-C. POTIER[1,2], C. ALBAC[1,2], F. STAGNI[3], M. GRILLI[4], E. SALVALAI[4], R. BARTESAGHI[3]
[1]CNRS INSERM UPMC, Paris, France; [2]ICM, Paris, France; [3]Dept. of Biomed. and Neuromotor Sci., Univ. of Bologna, Bologna, Italy; [4]Dept. Pharm. Sci, Un. Piemonte Orientale, Novara, Italy

Abstract: Down syndrome (DS), induced by trisomy of human chromosome 21 is the most common genetic cause of mental retardation. Cognitive deficits are a hallmark of the syndrome, both in individuals with DS and in mouse models such as the Ts65Dn. Neurogenesis impairment is present in Ts65Dn mice, starting at embryonic stages and extending to adulthood in the hippocampal dentate gyrus (Contestabile *et al.* 2007). Neurogenesis can be recovered after treatment with several molecules such as lithium, fluoxetine (Stagni *et al.* 2015) and TrkB agonist (Stagni *et al.* 2017). Here we tested three additional drugs selected for their ability to restore neurogenesis or cognitive deficits: i) a negative allosteric modulator selective for α5-containing $GABA_A$ receptors (α5IA, 5mg/Kg, Braudeau *et al.* 2011); ii) an agonist for the β2 adrenergic receptor (salmeterol, 1mg/Kg) that came out of a screen for FDA approved drugs reversing proliferation deficits in neural progenitors from Ts65Dn mice; iii) the neurotrophin IGF-1 1 (50 or 250µg/Kg, Castro *et al.* 2014).
Ts65Dn and WT neonates were treated daily from post-natal day 3 (P3) to post-natal day 15 (P15), then received BrdU (150mg/Kg), and were sacrificed 2 hours later. After cryoprotection and freezing, the brains were cut at 30µm and immunohistochemistry was conducted. BrdU positive cells were counted manually. For the salmeterol treated mice half brains were treated for Golgi staining using FD Rapid GolgiStain Kit (FD NeuroTechnologies).
We showed reduced number of BrdU positive cells in the dentate gyrus at P15 in Ts65Dn mice as compared to WT ($p= 0.013$). Treatment with α5IA from P3 to P15 did not correct neurogenesis deficits in Ts65Dn dentate gyrus ($p= 0.9054$) and had no effect in WT mice. Unexpectedly, the neurotrophin IGF-1 at 250µg/Kg decreased neurogenesis in WT mice ($p=0.0001$) but did not significantly improve Ts65Dn mice. At 50µg/Kg IGF-1 had no significant effect on neurogenesis in WT and Ts65Dn mice. Finally, salmeterol treatment is currently being analyzed both on neurogenesis and on the number of dendritic spines.
Our study showed no significant effect of α5IA on neurogenesis when administered during postnatal period (P3 to P15) at a procognitive dose, suggesting that GABAergic neurons might have different maturation in Ts65Dn mice as compared to WT. IGF-1 treatment that provided beneficial effects on mouse model of Rett syndrome that have reduced levels of IGF-1, did not increase neurogenesis in the Ts65Dn mice suggesting that IGF-1 levels in these mice might not be altered. Finally, we will present the results obtained on neurogenesis and dendritic spines following postnatal treatment with salmeterol.

Disclosures: M. Potier: None. **C. Albac:** None. **F. Stagni:** None. **M. Grilli:** None. **E. Salvalai:** None. **R. Bartesaghi:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.08/C16

Topic: A.07. Developmental Disorders

Support: Telethon TCP15021

Title: Discovery and characterization of novel selective NKCC1 inhibitors for Down syndrome and brain disorders with depolarizing GABAergic transmission

Authors: *A. SAVARDI[1,5], M. BORGOGNO[2,6], J. ORTEGA MARTÍNEZ[2], R. NARDUCCI[1], G. LA SALA[2], M. SUMMA[3], R. BERTORELLI[3], S. BERTOZZI[4], A. ARMIROTTI[4], A. CONTESTABILE[1], M. DE VIVO[2], L. CANCEDDA[1,7]
[1]Local Micro-Environment and Brain Develop. Lab., [2]Mol. Modeling and Drug Discovery Lab., [3]In Vivo Pharmacol. Facility, [4]Analytical Chem. Facility, Inst. Italiano di Tecnologia, Genova, Italy; [5]Univ. degli Studi di Genova, Genova, Italy; [6]Univ. degli Studi di Bologna, Bologna, Italy; [7]Dulbecco Telethon Inst., Roma, Italy

Abstract: Proper GABAergic transmission trough Cl-permeable $GABA_A$ receptors is fundamental for physiological brain development and function. Indeed, defective GABAergic signaling -due to a high ratio of expression of the Cl importer NKCC1 and Cl exporter KCC2- has been implicated in several neurodevelopmental disorders (e.g., Down syndrome, DS). Interestingly, NKCC1 inhibition by the FDA-approved diuretic bumetanide reverts cognitive deficits in the TS65Dn mouse models of DS and core symptoms in a number of models of other neurodevelopmental disorders. However, the required chronic treatment with bumetanide is burdened by its diuretic side effects caused by the antagonization of the kidney Cl importer NKCC2, which leads to hypokalemia and jeopardizes drug compliance. Crucially, these issues would be solved by selective NKCC1 inhibitors, thus devoid of the diuretic effect. Starting from bumetanide's structure, we applied a computational ligand-based approach to design new molecular entities that we tested *in vitro* for their capacity to selectively block NKCC1. Among the 3 newly-identified and highly promising NKCC1 inhibitors, one showed excellent solubility and metabolic stability *in vitro* and it was predicted to better penetrate the blood-brain barrier compared to bumetanide. Moreover, analysis of wild type mice systemically treated with this NKCC1 inhibitor revealed no diuretic effect. Finally, our novel, selective NKCC1 inhibitor was able to rescue cognitive deficits in Ts65Dn mice in four different memory tasks. Thus, a selective NKCC1 inhibitor devoid of the diuretic effects could represent a suitable and solid therapeutic strategy for the treatment of Down syndrome and all the brain disorders with depolarizing GABAergic transmission.

Disclosures: A. Savardi: None. **M. Borgogno:** None. **J. Ortega Martínez:** None. **R. Narducci:** None. **G. La Sala:** None. **M. Summa:** None. **R. Bertorelli:** None. **S. Bertozzi:** None. **A. Armirotti:** None. **A. Contestabile:** None. **M. De Vivo:** None. **L. Cancedda:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.09/C17

Topic: A.07. Developmental Disorders

Support: Fondation Jérôme Lejeune (Paris, France)
MINECO (SAF2013-49129-C2-1-R)
MINECO (MTM2015-64465-C2-1-R)
CDTI ("Smartfoods")
EU (Era Net Neuron PCIN-2013-060)
EMBO (short term EMBO fellowship)

Title: Overeating in a mouse model of Down syndrome is associated with a dopaminergic deficit in the prefrontal cortex

Authors: *M. FRUCTUOSO CASTELLAR[1,2], I. DE TOMA[2,3], K. LANGOHR[4,5], J. DAIROU[6], N. JANEL[6], M. DIERSSEN[2,3,4,7]
[1]Inst. Du Cerveau Et De La Moelle, Paris, France; [2]Cell. & Systems Neurobiology, Systems Biol. Program, Ctr. for Genomic Regulation (CRG), Barcelona, Spain; [3]Univ. Pompeu Fabra (UPF), Barcelona, Spain; [4]Human Pharmacol. and Clin. Neurosciences Res. Group, Neurosciences Res. Program,, Hosp. Del Mar Med. Res. Inst. (IMIM), Barcelona, Spain; [5]Dept. of Statistics and Operations Res., Univ. Politècnica De Catalunya/BarcelonaTech, Barcelona, Spain; [6]Unit of Functional and Adaptive Biol. (BFA), Univ. Paris Diderot, Sorbonne Paris Cité, CNRS UMR 8251, Paris, France; [7]Ctr. de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Barcelona, Spain

Abstract: Individuals with Down syndrome (DS) present high obesity prevalence that has been traditionally attributed to endocrine issues such as leptin resistance or thyroid gland dysfunction and deficient exercising. However, poor eating habits could also be a main contributor since individuals with DS consume regularly big amounts of energy-dense foods. As a matter of fact, DS brains show reduced volume and decreased functional connectivity of prefrontal cortex (PFC), a brain region implicated in reward and behavioral control. Here we hypothesized that the PFC impairment in DS individuals may increase their risk of overeating in environments with easy availability of sweet or fatty foods. To address this question, we characterized obesity development, meal pattern and food preferences in wild-type (WT) and Ts(1716)65Dn (Ts65Dn) mice, a DS mouse model, given both standard rodent chow and an energy- dense diet. Upon 8

weeks of free choice feeding, we investigated the appearance of compulsive and inflexible behaviors using stand-alone tests. Ts65Dn mice showed higher preference for energy-dense diets than WT mice and scored higher in compulsivity and inflexibility tests (limited access to energy-dense food and food adulteration with quinine hydrochloride). Both abnormal behaviors are associated with alterations in PFC function which depend, among other signals, on monoamines. Thus, we characterized the diet-induced changes in monoamine levels in prefrontal cortex and striatum, regions related to the reward-driven control of feeding, by high performance liquid chromatography (HPLC) that revealed reduced levels of dopamine in Ts65Dn mice that were PFC region-specific. Our results suggest that overeating of energy-dense foods might be more detrimental for behavioral control (e.g. flexibility, impulsivity management) in Ts65Dn mice and therefore, overeating might be a relevant contributor of obesity in DS.

Disclosures: M. Fructuoso Castellar: None. **I. de Toma:** None. **K. Langohr:** None. **J. Dairou:** None. **N. Janel:** None. **M. Dierssen:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.10/C18

Topic: A.07. Developmental Disorders

Support: PAPIIT-UNAM IN-304817
PAPIIT-UNAM IN-304417

Title: Cognitive decline in young and adults with Down syndrome

Authors: *O. GARCIA[1], E. M. RAMOS GALICIA[2], N. ARIAS TREJO[3]
[1]Facultad de Psicologia, UNAM, Mexico, D.F., Mexico; [2]Psicobiologia y Neurociencias, Facultad de Psicologia, UNAM, Ciudad de Mexico., Mexico; [3]Facultad de Psicologia, UNAM, Ciudad de Mexico, Mexico

Abstract: Down syndrome (DS) or trisomy 21 (Ts21) is the most common genetic cause of intellectual disability (ID). In addition, people with DS show an abnormally slow development in childhood and, subsequently, premature aging in adulthood accompanied by a cognitive decline and neuropathological characteristics of Alzheimer's disease (AD). However, most of the studies on aging in DS have focused on people over 40 years of age. Therefore, the objective of this work was to identify patterns of cognitive decline that could be indicators of accelerated aging in DS. Neuropsychological batteries CAMCOG-DS and Neuropsy Attention and Memory, were used to evaluate cognitive functions and detect mild degrees of cognitive impairment. Thirty individuals with DS with an age range of 10-30 years old divided into two groups of 10-20 years and 20-30 years participated in the study. We result show that people with an age range of 10-20

years have a good receptive language and expressive language, however, after 20 years show a decrease in expressive language and up to 30 years decreases the receptive language. The tests related to memory and learning and abstract thought show deficiencies from 20 years old. These results suggest that cognitive deficiencies can start from 20 years of age, with receptive language being one of the functions that can remain without apparent changes. The results of this work could contribute to design clinical strategies for evaluation and diagnosis of cognitive deterioration associated with aging in young population with Ts21.

Disclosures: O. Garcia: None. **E.M. Ramos Galicia:** None. **N. Arias Trejo:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.12/C20

Topic: A.07. Developmental Disorders

Support: ALANA USA Foundation (Contracts 124124 and 200381)
Alana CWRU/MIT Collaborative Fund
Awakening Angels Foundation
PSURG (Provost Summer Undergraduate Research Grant) at CWRU

Title: Effects of mild-to-moderate physical training on the gait dynamics of young Ts65Dn mice: A mouse model for Down syndrome

Authors: *M. STASKO[1], J. CHU[1], I. BASTEN[4], A. C. S. COSTA[2,3]
[2]Dept. of Pediatrics, [3]Dept. of Psychiatry, [1]Case Western Reserve Univ., Cleveland, OH; [4]Dept. of Child and Adolescent Psychiatry, Univ. Hosp. Brussels, Brussels, Belgium

Abstract: Delayed motor development and gait abnormalities have been observed in human beings with Down syndrome (DS), as well as in the Ts65Dn mouse model for DS. The immediate aim of this research was to test the development of gait dynamics in Ts65Dn mice using a DigiGait Apparatus (Mouse Specifics, Inc.). The device consists of a treadmill with a transparent belt in which gait dynamics can be quantified by analyzing images of the underside of the mice captured by high-speed video (181 frames/s). The image is rendered from the frame by software, and the areas of the paws are identified, vectorized, and used to calculate multiple variables of the gait. Here, performed longitudinal studies of 17 trisomic and 17 euploid mice, every other day, from 17 days until 35 days of age. Mice were allowed 5 minutes to acclimate, then practiced walking at four speeds (8, 12 ,16, and 18 cm/s) for 5 seconds each, with a short rest in between. After training, mice ran at belt speed of 18 cm/s for 30 seconds while video was recorded. Mice practiced at five higher speeds (22, 26, 30, 34, and 36 cm/s) for 5 seconds each with short rest intervals. Mice ran at belt speed of 36 cm/s for 30 seconds while video was

recorded. The following parameters were measured: duration and percent of swing, brake, propel, stance, and stride; and stride length, absolute paw angle, and stance width. For each of the parameters, two forelimb and two hindlimb values were averaged. Two-tailed T-tests were used to compare the means for each parameter between the two genotypes (Ts65Dn and euploid control). The main finding from these experiments was that Ts65Dn mice presented a 6-day delay in reaching the maximal speed of 36 cm/s when compared with euploid control littermates. However, when gait dynamics of the two groups of mice were compared by assessing gait characteristics at 35 days of age, we found no significant differences between genotypes. This result contrasted with our previous finding showing various DS-like alterations in gait dynamics in Ts65Dn mice (Hampton at al., Physiol Behav 82:381-389, 2004). Therefore, we hypothesized that, by exposing them to intervals of moderate physical training from an early age, Ts65Dn mice were able to reach euploid control-level performance by 35 days of age. We are currently testing this hypothesis by testing naïve Ts65Dn and control mice at 21, 29, and 35 days of age. Preliminary data collected from 35-day old naïve mice, did reproduce our previous findings and showed that even every-other-day, mild-to-moderate degree of physical training can significantly increase stride length and decreased stride frequency in Ts65Dn mice.

Disclosures: M. Stasko: None. **J. Chu:** None. **I. Basten:** None. **A.C.S. Costa:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.13/C21

Topic: A.07. Developmental Disorders

Support: NIH Grant 1RF1AG057355
NIH 1R01AG041135
LuMind
Point Rider Foundation

Title: Systematic functional analysis of 21st chromosome genes using *C. elegans*

Authors: *J. T. PIERCE, S. M. SANCHEZ, S. NORDQUIST, S. R. SMITH
Univ. of Texas at Austin, Austin, TX

Abstract: Down syndrome, caused by trisomy of the 21st chromosome, leads to lifelong cognitive impairment. Efforts to understand this disorder first require an understanding of the genes encoded on the 21st chromosome (HSA21). While progress has been made using traditional mouse models, the tiny nematode *C. elegans* represents a complementary model to uncover the in vivo function of genes. We analyzed all 213 predicted protein-coding genes on HSA21 and found that, excluding the keratin genes, approximately half had orthologs

represented in worm. Using RNAi and loss-of-function mutants, we systematically investigated the role of all orthologs in viability and neuronal function. Overall, we identified ten HSA21 orthologs that are required for neuromuscular behaviors: *cle-1* (*COL18A1*), *cysl-2* (*CBS*), *dnsn-1* (*DONSON*), *eva-1* (*EVA1C*), *mtq-2* (*N6ATM1*), *ncam-1* (NCAM2), *pad-2* (*POFUT2*), *pdxk-1* (*PDXK*), *rnt-1* (*RUNX1*), and *unc-26* (*SYNJ1*). We also found that three of these genes are required for normal release of the neurotransmitter acetylcholine. This includes a known synaptic gene unc-26 (*SYNJ1*), as well as uncharacterized genes *pdxk-1* (*PDXK*) and *mtq-2* (*N6ATM1*). Furthermore, we found that the glutamine methyltransferase MTQ-2 localizes to cholinergic synapses where it appears to regulate neurotransmission via methylation of a Gα/o signaling protein. As the first systematic functional analysis of HSA21 orthologs, our study may serve as a platform to understand genes that underlie phenotypes associated with Down syndrome.

Disclosures: J.T. Pierce: None. **S.M. Sanchez:** None. **S. Nordquist:** None. **S.R. Smith:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.14/C22

Topic: A.07. Developmental Disorders

Title: Spinogenesis impairment can be rescued by neonatal treatment with a beta 2-adrenergic agonist in a mouse model of Down syndrome

Authors: *F. STAGNI[1], M. SALVALAI[2], B. UGUAGLIATI[1], M. EMILI[1], S. GUIDI[1], A. GIACOMINI[1], V. BORTOLOTTO[2], M. GRILLI[2], R. BARTESAGHI[1]
[1]Dept. of Biomed. and Neuromotor Sci., Univ. of Bologna, Bologna, Italy; [2]Dept. of Pharmaceut. Sci., Univ. of Piemonte Orientale, Novara, Italy

Abstract: Down syndrome (DS) is a relatively high-incidence (1:700/1000) genetic condition due to triplication of chromosome 21. The intellectual disability (ID) that characterizes DS is attributable to impairment in the processes of neurogenesis and spinogenesis. It ensues that drugs that are able to increase the number of neurons and/or spine density may be regarded as possible strategic tools to improve brain ID in DS. The goal of this study was to establish whether it is possible to pharmacologically improve brain development in DS by exploiting the Ts65Dn mouse, the most popular model of DS. We recently screened two libraries of FDA-approved drugs in neural progenitor cells (NPCs) derived from Ts65Dn mice for a drug-repurposing project. Among the tested drugs, we found that the beta 2-adrenergic agonist clenbuterol increased neurogenesis and favored neuron maturation. We then progressed to *in vivo* experiments and examined the effect of treatment on the hippocampal dentate gyrus, a region that is fundamental for declarative memory and that largely develops in the early postnatal period. Ts65Dn and euploid pups received clenbuterol (10 µg/kg, 0.5 mg/kg, 1 mg/kg or 2

mg/kg; s.c. daily injections) from postnatal day 3 (P3) to P15. On P15 mice received an injection of BrdU, in order to label NPCs, and were killed 2h later. We found that in Ts65Dn mice all doses of clenbuterol caused a large increase in the density of dendritic spines of the principal neurons of the dentate gyrus that became even larger than in untreated euploid mice. While the three lower doses of clenbuterol did not affect proliferation, the highest dose was able to increase the number of BrdU-positive cells, although in a marginally significant manner. This study provides novel evidence that treatment with the beta 2-adrenergic agonist clenbuterol is able to fully restore spinogenesis in the hippocampal dentate gyrus. The finding that this effect took place with a low dose of clenbuterol appears of relevance from a translational viewpoint because the use of low doses may reduce the probability of effects on beta 1-adrenergic receptors. The effect of clenbuterol on neurogenesis took place with the highest tested dose only, suggesting that it may not be a drug of choice for restoration of neurogenesis in DS. On the other hand, various drugs with a safe profile have been shown to be able to restore neurogenesis in the Ts65Dn model of DS. Taken together, these data suggest that co-treatment with clenbuterol and a drug that restores neurogenesis may represent a strategy for the improvement of the two major defects of the DS brain: hypocellularity and spine hypotrophy.

Disclosures: F. Stagni: None. **M. Salvalai:** None. **B. Uguagliati:** None. **M. Emili:** None. **S. Guidi:** None. **A. Giacomini:** None. **V. Bortolotto:** None. **M. Grilli:** None. **R. Bartesaghi:** None.

Poster

640. Down Syndrome

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 640.15/C23

Topic: A.07. Developmental Disorders

Title: Developmental alterations in the subiculum of fetuses with Down syndrome and in the Ts65Dn model of Down syndrome

Authors: *S. GUIDI[1], F. STAGNI[1], A. GIACOMINI[1], M. EMILI[1], B. UGUAGLIATI[1], M. BONASONI[2], R. BARTESAGHI[1]
[1]DIBINEM - Dept. Biomed. and Neuromotor Sci., Bologna Univ., Bologna, Italy; [2]Pathology Unit, Azienda Unità Sanitaria Locale, IRCCS, Reggio Emilia, Italy

Abstract: Intellectual disability (ID) is an invariable hallmark of Down syndrome (DS), a genetic condition due to triplication of chromosome 21. Accumulating evidence suggests that ID is attributable to widespread neurogenesis impairment during critical windows of prenatal development. Consequently, children with DS are impaired in various cognitive domains, including explicit memory. Consistently with memory alterations, fetuses with DS exhibit neurogenesis impairment in the hippocampus, a region fundamental for long-term explicit

memory. While the hippocampus is involved in memory formation and consolidation, recent evidence suggests that the subiculum plays a unique role in memory retrieval, a process that also appears to be altered in DS. While much attention has been devoted to the hippocampus, there is a striking lack of information regarding the subiculum of individuals with DS and DS models. In order to fill this gap, in the current study we examined the subiculum of fetuses with DS, with the goal to establish whether it exhibits developmental alterations that may account for the damage of subiculum-dependent memory functions in children with DS. We additionally examined the subiculum of the Ts65Dn mouse, a widely-used model of DS, in order to obtain comparative information. Fetal brains (17-21 weeks of gestation) were obtained according to procedures approved by the Ethical Committee of the St. Orsola-Malpighi Hospital, Bologna, Italy. We found that the subiculum of DS fetuses had a reduced size and a reduced number of cells. An evaluation of the number of neural progenitor cells (NPCs) in the ventricular zone of the subiculum showed that fetuses with DS had a reduced number of NPCs, which can account for the subicular hypocellularity. An evaluation of the phenotype of the cells populating the subiculum showed that fetuses with DS had a reduced percentage of neurons and an increased percentage of astrocytes, indicating impairment in the acquisition of a neuronal phenotype. In addition, fetuses with DS had an increased percentage of cells immunopositive for calretinin, a calcium-binding protein expressed by inhibitory interneurons. Similarly to fetuses with DS, the subiculum of neonate Ts65Dn mice was reduced in size, had a reduced number of neurons and a reduced number of proliferating cells. Results suggest that the developmental defects in the subiculum of DS fetuses may underlie impairment in recall memory and possibly other functions played by the subiculum. The finding that the subiculum of the Ts65Dn mouse exhibits neuroanatomical defects resembling those seen in fetuses with DS further validates the use of this model for preclinical studies.

Disclosures: S. Guidi: None. **F. Stagni:** None. **A. Giacomini:** None. **M. Emili:** None. **B. Uguagliati:** None. **M. Bonasoni:** None. **R. Bartesaghi:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.01/C24

Topic: A.07. Developmental Disorders

Support: NIH Grant
NSF GRFP

Title: Altered motor function and perseverative behaviors in a mouse model of a human gain-of-function mutation in the GRIK2 kainate receptor gene

Authors: *E. BINELLI[1], T. NOMURA[2], W. P. NOBIS[3], J. R. STOLZ[1], A. CONTRACTOR[4], G. T. SWANSON[1]
[1]Pharmacol., [2]Physiol., [3]Neurol., Northwestern Univ., Chicago, IL; [4]Physiol., Northwestern Univ. Dept. of Physiol., Chicago, IL

Abstract: Kainate receptors (KARs) are a family of ionotropic glutamate receptors with diverse roles in the central nervous system. Missense mutations in GRIK genes, which encode KAR subunits, can lead to profound neurodevelopmental disorders if they result in aberrant or reduced receptor function. To gain insight into the synaptic and circuit disruptions that occur in children with KAR genetic variants, we generated a mouse model for a gain-of-function GRIK2 mutation in a child with developmental delay, ataxia, and profound language deficits. The mutation results in a threonine substitution for alanine at position 657 in the GluK2 subunit, which profoundly alters the gating properties of KARs incorporating the mutant subunit. Here we report the initial behavioral and synaptic phenotypes of the GluK2(A657T) mouse model.
We generated the GluK2(A657T) knock-in mouse line using CRISPR/Cas9 gene editing. Heterozygous mice displayed early onset ataxia with otherwise grossly normal development. Homozygous mice were not viable. Behavioral tests were performed on wild type and heterozygous littermates in order to test motor function, social interaction, anxiety, and perseverative behaviors. Juvenile GluK2(A657T)+/- mice performed significantly worse in tests of motor coordination when compared to wildtype littermates and did not exhibit typical perseverative behaviors such as nestlet shredding and marble burying. In contrast, wildtype and heterozygous mice showed no differences in open field and zero maze tests. We confirmed that the mutant GluK2(A657T) subunit was incorporated into functional KARs in whole cell recordings from mossy fiber-CA3 pyramidal cell synapses; KAR-EPSCs in GluK2(A657T)+/- neurons decayed with a significantly slower time course compared to those in wildtype littermates (mean $\boldsymbol{\tau}$; of 172.4 ms ± 30.9 ms and 35.3 ms ± 1.3 ms, n=5 and 3, respectively). The longer time course of KAR activation suggests that integrative properties of CA3 pyramidal neurons will differ in the mutant mice. Additional behavioral, synaptic and circuit analysis are underway. In summary, these results suggest that the GluK2(A657T) mouse successfully models several aspects of the patient's syndrome and identify at least one potentially pathological synaptic dysfunction.

Disclosures: E. Binelli: None. **T. Nomura:** None. **W.P. Nobis:** None. **J.R. Stolz:** None. **A. Contractor:** None. **G.T. Swanson:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.02/C25

Topic: A.07. Developmental Disorders

Support: 1R01NS084398

Title: Genomic aberrations in embryonic neural progenitor cells may underlie cellular pathologies of lysophosphatidic acid induced hydrocephalus in mice

Authors: *W. S. MCDONALD, J. CHUN
Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: Fetal post-hemorrhagic hydrocephalus (PHH) is a rare but devastating disease that's associated with debilitating neurodevelopmental disorders and infant mortality. The etiology of fetal PHH remains unclear and there are no curative therapies, with major treatments limited to palliative, surgical approaches. Our research group has identified the involvement of lysophosphatidic acid (LPA), a bioactive and blood-derived lysophospholipid, through its G protein-coupled receptor LPA1, in PHH pathogenesis. Our LPA-induced model of PHH recapitulates many pathological features of hemorrhagic injury identified in clinical hydrocephalus including cortical cell loss, neural progenitor cell (NPC) lineage changes (including ependymal cell loss), ciliary dysfunction and/or loss, choroid plexus dysfunction and intracranial fluid imbalances (1). Moreover, we also observed alterations in genomic content, at the cellular level, in our model of PHH. Genomic abnormalities (i.e. aneuploidies) have also been identified 8-16% of congenital hydrocephalus cases and predict a higher risk of poor clinical outcomes as well as comorbid neurological disorders (i.e., schizophrenia, and Down syndrome) (2-7). Approach: To assess the potential genomic component of fetal PHH, fetal mice received intraventricular injections of LPA or vehicle (HBSS). DNA content by flow cytometry and cytogenetics approaches were used to determine genomic changes in embryonic cortices during fetal and early post-natal development. To assess the link between genomic aberrations and functionality of NPCs, we performed microelectrode array (MEA) recording during differentiation of neurons harvested from cortices of vehicle and LPA-exposed embryos. Results: Our results show acute changes in chromosomal content in cortical progenitor cells after LPA exposure. Prolonged aberrations in the genomes of neural progenitor cells are also observed, by flow cytometric genomic content analysis. Our MEA data suggests that LPA exposure prolongs network formation. The results indicate that LPA exposure during embryonic development alters function of progenitor cells and these changes are linked to prolonged genomic abnormalities in NPCs. LPA signaling may be a molecular initiator of genomic and cellular pathologies in murine hydrocephalus.

Disclosures: W.S. McDonald: None. **J. Chun:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.03/C26

Topic: A.07. Developmental Disorders

Support: DNS Operating Grant

Title: Conserved role of DNM1in circadian rhythm control in humans and *Drosophila*

Authors: *F. V. BOLDUC[1], R. HE[2], C. ROSENFELT[2]
[1]Div. Pediatric Neurosci, [2]Univ. of Alberta, Edmonton, AB, Canada

Abstract: Background: Dynamin-1 (DNM1) is a conserved, large guanosine triphosphatase (GTPase) essential to synaptic vesicle recycling via clathrin-mediated endocytosis. De novo missense mutations in the *DNM1* gene have been identified in patients with severe epileptic encephalopathy and more recently, intellectual disability. However, the role of *DNM1*in sleep has not been reported before. Considering the importance of sleep on memory formation and the significant impact of sleep disorders on quality of life for individuals and their families, we sought to explore this further. Methods: We used whole exome sequencing (WES) in individuals with developmental delay and seizure to identify disorder causing variants. Standardized cognitive testing was used. Sleep questionnaires were used to identify sleep issues. Next, we used Drosophila temperature sensitive alleles of the gene identified via (WES) to assess the functional effect of the gene in various behaviors. Results: We identified two novel cases of *DNM1* mutations associated with a seizure disorder and intellectual disability, but also sleep disturbances. Whole exome sequencing revealed a previously reported de novo missense mutation c.709C>T (p.Arg237Trp) in one patient, while the other patient with a similar but less severe phenotype was found to have an in frame deletion c.647_655del (p.Asp215_Arg217del) in exon 5 of *DNM1*. Intragenic deletions in *DNM1* have not been previously reported. Those patients presented both with sleep dysregulation. Importantly, using a well-established locomotor assay for circadian activity, we also identified significant disturbance of circadian behavior in the *Drosophilamelanogaster* ortholog mutant of *DNM1*, *shibire*. Employing a pathway analysis approach we further identified potential genetic networks that could underlie both the seizure and circadian defects observed in individuals and flies with *DNM1* variation. Conclusions: Together, our results show that *DNM1*needs to be considered as a candidate gene for patients with a wide range of seizure severity, intellectual disability but also sleep and circadian disturbances.

Disclosures: R. He: None. **C. Rosenfelt:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.04/C27

Topic: A.07. Developmental Disorders

Support: Miscelaneous Friedman Research Fund

Title: Subconvulsive stimulation in early postnatal life reduces NeuN and parvalbumin antigenicity while increasing interneuronal activity within the dentate gyrus and amygdala cortical complex in juvenile rats

Authors: *L. K. FRIEDMAN[1], B. A. KAHEN[1], J. E. HOFFMAN[2]
[2]Cell Biol., [1]New York Med. Col., Valhalla, NY

Abstract: Although select genes have been identified in cases of severe ASD, they do not yet account for the mild and more functional ASD cases that are not pervasive until years after birth. We hypothesized that continuous subconvulsive activity in early postnatal life may contribute to the development of autistic pathologies. To establish a valid ASD model, daily subconvulsive step-up doses of kainic acid (KA) were administered subcutaneously to rat pups for 15 days beginning on postnatal (P) day 6. At 24 h after the last subconvulsive treatment, a single convulsive dose of KA was administered to ASD (ASD+KA) and naïve rat pups (1xKA) to compare cellular consequences of subconvulsive vs. convulsive activity in early postnatal life. Brains were histologically evaluated with cresyl violet, NeuN, *cfos* and parvalbumin (PV) immunohistochemistry. The ASD group had increased numbers of hyperbasophilic neurons within the amygdala cortical complex (AMG/Cx) that correlated with reduced NeuN antigenicity revealing an increased average gap width extending from the BLA/BSTA to the piriform and entorhinal cortices, but in the absence of cell loss (142 ± 5 µm vs. 216 ± 8 µm, $p<0.01$). Serial hippocampal sections were devoid of injury in contrast to juveniles with 1xKA. Few cells were *cfos*$^+$ in control AMG/Cx, whereas the ASD group had many scattered *cfos*$^+$ cells within the AMG/Cx and dorsal blade of the dentate gyrus (DG), presumably GABAergic interneurons (2.33 ± 1.8 vs. 34.3 ± 4.4, $p<0.001$). A prominent *cfos*$^+$ cluster was also observed within the BSTA (45.5 ± 1.5, $p<0.002$). After ASD+KA, extremely dark *cfos* expression was apparent within large cells of the hilus, resembling GABAergic mossy cell distribution. Eosinophilia was also detected deep within the hilus, but belonged to a different cell population. Interneurons expressing PV were dramatically reduced in number and immunodensity but only in ASD and ASD+KA treated groups. Data suggest that continuous subconvulsive stimulation of high density low-affinity KA receptors of AMG/Cx in early postnatal life results in persistent or delayed elevations in activity within certain GABAergic interneurons of the AMG/Cx and DG. A progressive hyperactive state in early life due to a steady loss of PV interneuronal inhibition in these regions could lead to autistic pathologies. Accordingly, lack of NeuN antigenicity appears to reflect changes in metabolic activity rather than neuronal cell loss which may be sufficient to produce a mild and functional ASD syndrome.

Disclosures: L.K. Friedman: None. **B.A. Kahen:** None. **J.E. Hoffman:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.05/C28

Topic: A.07. Developmental Disorders

Support: Miscellaneous Friedman Research Fund

Title: Postnatal-induced autism impairs social behavior and hovering in juvenile rats

Authors: *B. A. KAHEN, L. K. FRIEDMAN
New York Med. Col., Valhalla, NY

Abstract: The overall diagnosis of autism spectrum disorder (ASD) varies widely from very mild to severe social and cognitive impairments. We hypothesized that subconvulsive activity in early postnatal life may contribute to the development of autistic behavior. To induce a subconvulsive postnatal ASD model, daily step-up doses of kainic acid (KA) were administered subcutaneously to rat pups for 15 days beginning on postnatal (P) day 6 to elevate early life neuronal hyperactivity. Handling, open field, elevated plus maze, social interaction, object recognition and several hovering tests were examined 24 h after the last subconvulsive treatment. Within 5 days, increased exploratory and escape behavior in the handling test were observed in both sexes. On testing day P21, ASD females were more active in the elevated plus maze. In contrast, the social interaction test revealed that the ASD males spent more time and visits to the novel object and less time and visits with the stranger compared to controls (12.56s ± 3.97 vs. 17.09s ± 6.32, $p = 0.037$). The female ASD group was more active but otherwise similar to controls. To evaluate group dynamics, a novel hovering test was developed whereby rat pups from same groups and different groups were allowed to socialize in a small rectangular, large rectangular, or circular environment. Control pups hovered quickly and more frequently in all three environments whether they socialized with littermates or with other age-matched controls from a different litter (onset of hovering, 75s vs. 105s). In the circular environment, the ASD pups failed to group in large numbers. There was also an increased latency to hovering in the ASD group when tested with littermates in the large rectangular environment, but when a second ASD group was introduced to the first ASD group, wild running occurred and much less grouping was observed. In the spontaneous alternating T-Maze test, males exhibited more repetitive behavior. The object recognition test showed that only the ASD males spent less time with both old and new objects (4.09s ± 1.85 vs. 11.82s ± 2.85, $p= 0.038$). These findings suggest that continuous excitation of low-affinity KA binding sites in early postnatal life leads to increased hyperactivity and an ASD phenotype in the juvenile period. Males were more susceptible to developing autistic behaviors and cognitive pathologies, validating our postnatal model for autism.

Disclosures: B.A. Kahen: None. **L.K. Friedman:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.06/C29

Topic: A.07. Developmental Disorders

Support: Estonian Research Council (institutional research funding IUT19-18)
European Union through the European Regional Development Fund (Project No. 2014-2020.4.01.15-0012)
Pitt Hopkins Research Foundation and Million Dollar Bike Ride Pilot Grant Program for Rare Disease Research at UPenn Orphan Disease Center (grants MDBR-16-122-PHP and MDBR-17-127-Pitt Hopkins)

Title: Silencing of *Drosophila* ortholog of TCF4 leads to behavioural impairment

Authors: *L. TAMBERG, M. JAAGO, A. SHUBINA, T. TIMMUSK, M. PALGI
Tallinn Univ. of Technol., Tallinn, Estonia

Abstract: Pitt-Hopkins syndrome (PTHS) is a rare intellectual disability syndrome characterized by specific facial features, severe mental retardation, lack of speech, and breathing problems. PTHS is caused by haplo-insufficiency of Transcription factor 4 (TCF4). TCF4 is one of the three human class I basic helix-loop-helix transcription factors also called E-proteins. In *Drosophila* there is a sole E-protein Daughterless (Da). We have previously shown that Da is the functional homolog of TCF4, that human TCF4 can replace Da in fly nervous system development and that the same homologous PTHS associated mutations cause similar effects in TCF4 and Da. We have used CRISPR-Cas9 technology for introducing FLAG tag to Da locus undisturbing the protein function , which allows us to study Da expression, since there is no good available antibodies for Da. Our new data demonstrates that lowered levels of Da in the nervous system of *Drosophila* larvae impair appetitive olfactory learning or in the adults affect negative geotaxis. These phenotypes can be used as a model for screening potential treatments for PTHS. Our latest results will be presented.

Disclosures: M. Jaago: None. **A. Shubina:** None. **T. Timmusk:** None. **M. Palgi:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.07/C30

Topic: A.07. Developmental Disorders

Title: CHD7 controls cerebellar development and granule cell differentiation

Authors: *N. REDDY[1], S. MAJIDI[1], C. J. FERGUSON[1], J. V. GOODMAN[1], T. YAMADA[1], A. BONNI[2]
[1]Washington Univ. in St. Louis, Saint Louis, MO; [2]Dept. of Neurosci., Washington Univ. in St. Louis, Sch. of Medi, Saint Louis, MO

Abstract: Proper brain development and neuronal differentiation are the result of precise temporal control of gene expression. Additionally, neurodevelopmental disorders and diseases, as well as premature death, are often due to genetic perturbations affecting gene expression programs. In particular, homozygous chromatin remodeling protein mutations tend to be embryonically lethal, while heterozygous mutations resulting in haploinsufficiency cause disease. Specifically, de novo mutations in CHD7, a member of the chromodomain helicase DNA-binding (CHD) family of ATP-dependent chromatin remodeling proteins, lead to CHARGE (coloboma of the eye, heart defects, atresia of the choanae, retardation of growth/development, genital and ear abnormalities) syndrome. Interestingly, CHD7 haploinsufficiency has also been shown to cause cerebellar hypoplasia and/or foliation defects in CHARGE patients. These phenotype suggests a critical role of CHD7 in multiple aspects of granule cell developmental programs, yet the distinct roles of CHD7 behind these phenotypes remains to be revealed.
In order to answer these questions, we have conditionally knocked out CHD7 in granule cell precursor cells of the mouse cerebellum. We aim to characterize the cellular phenotypes that result from the knockout of CHD7 in granule cell precursors. To better understand the mechanistic role of CHD7 and gene programs that CHD7 regulates we will intersect changes in the epigenetic state and transcriptional environment of immature granule cells in the presence and absence of CHD7. The described experiments will lend insight to the underlying developmental disruptions caused by CHD7 knockout, the multiple roles of CHD7 in granule cell development, and the mechanism by which CHD7 orchestrates these developmental and transcriptional programs.

Disclosures: N. Reddy: None. **S. Majidi:** None. **C.J. Ferguson:** None. **J.V. Goodman:** None. **T. Yamada:** None. **A. Bonni:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.08/C31

Topic: A.07. Developmental Disorders

Support: NSF GRFP to RTB

Title: Paternal ethanol exposure prior to conception impacts offspring brain and behavioral development

Authors: *K. E. CONNER[1], R. T. BOTTOM[1], K. J. HUFFMAN[1,2]
[1]Interdepartmental Neurosci. Program, [2]Dept. of Psychology, Univ. of California, Riverside, CA

Abstract: Ethanol exposure *in utero* can cause cognitive, behavioral, and sensorimotor deficits in offspring. Past research has predominantly focused on prenatal ethanol exposure (PrEE) from maternal consumption of alcohol during pregnancy. However, little is known about how paternal ethanol exposure, prior to conception, may impact offspring development. Ethanol can alter epigenetic profiles of sperm, presenting a potential mechanism for impacting offspring development via paternal ethanol consumption. Our laboratory recently documented transgenerational transmission of stable genetic and neuroanatomical phenotypes in neocortex, as well as behavioral effects, resulting from PrEE (Abbott et al., 2017). Because our transgenerational model passes epigenetic modifications via male sperm, we hypothesized that paternal ethanol exposure before conception (PatEE) may impact neocortical development in offspring. Thus, we generated a PatEE mouse model where experimental male mice were given 25% ethanol in water for 15-23 days prior to mating. Offspring of males exposed to either ethanol (PatEE) or water (control) were examined at postnatal (P) day 0 for brain phenotypes. There were no differences between control and PatEE mice in measures of brain weight or neocortical length. Neuroanatomy was analyzed via Nissl staining which revealed no significant differences in cortical thickness between the two offspring groups. RNA *in situ* hybridization was used to investigate expression of two genes, *Id2* and *RZRβ,* which are critical to patterning the connections of the neocortex, in control and PatEE brains. Laminar-specific patterns of gene expression were found in both groups, where *Id2* was expressed rostromedially and *RZRβ* rostrolaterally. However, expression boundaries were shifted laterally in *Id2* and medially *RZRβ* in PatEE mice. Lipophilic dyes were used to observe intraneocortical (INC) development in putative somatosensory and visual cortices of control and PatEE P0 brains. Abnormal, overlapping labeling of INCs from the two distinct cortical regions was seen at the somatosensory-visual boundary in PatEE but not control mice. This region corresponded to the area of shifted neocortical gene expression. Finally, two subsets of pups were raised to ages P20 and P30 and tested on behavioral assays. PatEE mice exhibited increased motor deficits and

hyperactivity compared to controls, as assessed by Suok and Rotarod tests. Overall, these findings suggest that ethanol exposure in males prior to conception may induce long-lasting changes in brain and behavior of their offspring.

Disclosures: K.E. Conner: None. **R.T. Bottom:** None. **K.J. Huffman:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.09/C32

Topic: A.07. Developmental Disorders

Support: NSF Graduate Research Fellowship to RTB

Title: Neuro-behavioral effects of prenatal ethanol exposure in pre-pubescence: A transgenerational mouse model of FASD

Authors: *R. T. BOTTOM[1], O. O. KOZANIAN[2], D. J. ROHAC[2], K. J. HUFFMAN[2,1]
[1]Neurosci., [2]Psychology, Univ. of California, Riverside, Riverside, CA

Abstract: Ethanol consumption during pregnancy results in detrimental developmental outcomes in offspring which often persist into adulthood. Fetal alcohol spectrum disorders (FASD) is an umbrella term that describes the range of developmental outcomes caused by prenatal ethanol exposure (PrEE). Children and adults with FASD may have neurobiological, cognitive and behavioral deficits that can potentially be transmitted across generations to unexposed offspring. The cognitive and behavioral deficits present in FASD have led researchers to generate hypotheses centering around dysfunction of the neocortex, as it is the primary structure responsible for complex, higher-order functions. Recently, our laboratory generated a transgenerational mouse model of FASD and demonstrated the transmission of PrEE-related phenotypes, such as ectopic intraneocortical connectivity and altered gene expression in the neocortex of newborn, postnatal day (P) 0 mice and adverse behavioral outcomes in peri-pubescence (P30), to the unexposed third generation (Abbott et al., 2017). The current study extends this work by examining whether PrEE-related brain phenotypes observed in newborn PrEE mice are maintained throughout 'childhood' (to age P20) and whether these phenotypes pass to subsequent generations. Specifically, we investigated if ectopic intraneocortical connections (INCs) found in first generation (F1) PrEE newborns (El Shawa et al., 2013) persist into pre-pubescence (P20) and whether these phenotypes are present at P20 transgenerationally. We found that PrEE-induced ectopic cortical connectivity observed in newborn F1 mice is rescued by P20, and is not present in F2 or F3 P20 animals. *In situ* hybridization for *Id2* and *RZRβ* was employed to assess gene expression in the neocortex, where layer and region specific patterns were observed in all groups of mice. Lastly, using a battery of behavioral assays, we

found that PrEE mice of F1, F2 and F3 generations continue to show significant behavioral deficits at P20 including poor motor coordination, sensorimotor integration, and depression-like behavior. These results indicate the persistence of PrEE-induced developmental outcomes into pre-pubescence, as well as their ability to be transmitted across generations. Results from this study will help identify long-term neurobiological and behavioral effects resulting from prenatal ethanol-exposure related brain dysfunction in humans with FASD and their kin.

Disclosures: R.T. Bottom: None. **O.O. Kozanian:** None. **D.J. Rohac:** None. **K.J. Huffman:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.10/C33

Topic: A.07. Developmental Disorders

Support: Intramural NIH Grant Z01 NS003041-11

Title: A spontaneous marmoset model of dysgenesis of the corpus callosum

Authors: D. SZCZUPAK[1], C. LIU[1], C. C. YEN[1], R. LENT[3], F. F. TOVAR-MOLL[3], *A. C. SILVA[2]
[1]NINDS, NIH, bethesda, MD; [2]NINDS, NIH, Bethesda, MD; [3]Inst. D'or for Res. and Educ., Rio de Janeiro, Brazil

Abstract: Dysgenesis of the corpus callosum (DCC) is a unique condition caused by a congenital malformation in this structure. It can vary from complete, to partial dysgenesis or simply hypoplasia. This variety of phenotypes result in several different clinical presentations. While some of these patients are perfectly normal and cognitively well preserved, most have a subnormal IQ coefficient, with a subset of those being severely compromised and needing caretakers' assistance. The underlying mechanisms that cause the symptoms in a portion of these patients are still unknown. Many mouse models have been used to study this pathology, but rodents' brain anatomy and function are very different from humans. To evaluate more cognitive tasks to understand how the underlying anatomy contributes to the cognition, a better suited animal model is needed. Here we present the characterization of the first case of spontaneous corpus callosum hypoplasia in a non-human primate, the common marmoset (Callithrix jacchus). Using *in vivo* diffusion tensor MRI with 2 shells (b=1000/2000 s/mm2, 64/128 directions respectively), blip up and blip down, isotropic spatial resolution = 0.5mm, we were able to reconstruct the entire brain connectivity and see abnormal formation of the corpus callosum in one male marmoset 6.5 years old (Figure 1). These abnormalities were also observed in 3D T1- and T2-weighted MRI of the same animal. We then proceeded to retrospectively search MRI

scans from relatives of the affected marmoset, and we found 1 other with similar malformations in the same lineage, confirming that the congenital defect has an inheritable cause. Our results indicate that marmosets are a promising animal model for spontaneous presentations of malformation s of the corpus callosum.

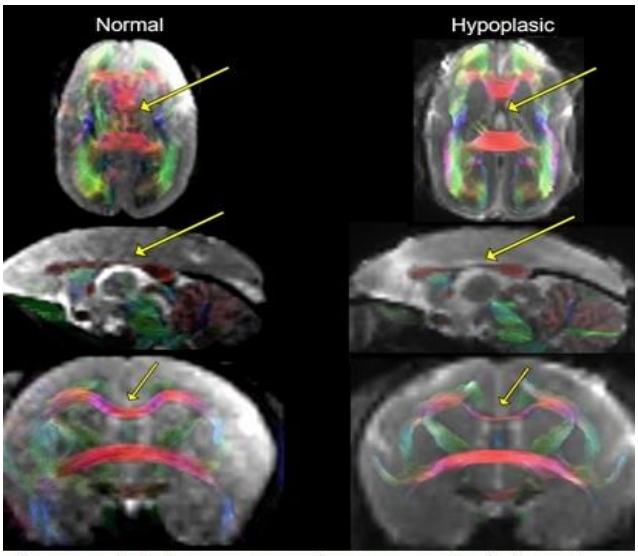


Figure 1. Whole brain tractography in a normal and a hypoplasic marmoset in 3 different planes. Arrows show the thinning of the body of the CC.

Disclosures: D. Szczupak: None. **C. Liu:** None. **C.C. Yen:** None. **R. Lent:** None. **F.F. Tovar-Moll:** None. **A.C. Silva:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.11/C34

Topic: A.07. Developmental Disorders

Support: R37 AA08757

Title: Binge-like alcohol produces long-lasting epigenetic marks on the stress axis only during the prenatal to prepubertal period but not after puberty

Authors: G. BERGER[1], L. CHASTAIN[1], O. GANGISETTY[1], V. MURUGAN[1], M. CABRERA[1], *D. K. SARKAR[2]
[1]Endocrinol. and Animal Biosci. Grad. Program, Rutgers Univ., New Brunswick, NJ; [2]Rutgers, SUNJ, New Brunswick, NJ

Abstract: Alcohol exposure during prenatal and postnatal periods can impact developmental pathways resulting in lasting structural and regulatory changes that predispose individuals to diseases including hyper-responsiveness to stress with exaggerated circulating glucocorticoids and enhanced anxiety like behaviors. Recently, it has been shown that alcohol exposures during the adolescent periods similarly predisposes individuals to adulthood stress abnormalities and enhanced anxiety. This raises the question of developmental timing: when does alcohol programming of stress axis to hyper-response cease? To address this issue, we fed young rats at various stages of reproductive development (postnatal period 2-7 days of age; juvenile periods, 15-20 days of age; prepubertal period 23-28 days of age; or post-pubertal period 50-55 days age) with a liquid diet containing 11.34% alcohol to raise blood alcohol levels to a range of 150-200mg/dl. Control animals were pair-fed an isocaloric volume of maltose dextrin. These rats were maintained in the animal house and challenged with restraint stress around 65 days of age. The stress challenge was conducted in both sexes. For females, the stress study was conducted on diestrus. Several days after the stress response, animals were sacrificed and the hypothalamic tissue samples were obtained and used for measurements of gene expression and methylation or left alone until PD 90, when animals underwent open field behavioral testing to measure anxiety and locomotor activity. Plasma glucocorticoid levels after restraint demonstrated an enhanced response to restraint stress in adult male and female rats who were given alcohol either on postnatal, juvenile or prepubertal period but not after pubertal period. Among pre-pubertal time groups, males displayed increased hyperactivity defined by increased distance moved and increased time mobile across pre-pubertal age groups when compared to pair-fed controls. Females displayed increased anxiety-like behaviors defined by decreased central tendency and increased avoidance behavior when compared to pair-fed controls. Since proopiomelanocortin*(Pomc)* is known to be an inhibitory regulator of the stress axis, we measured the expression of *Pomc* mRNA and DNA methylation levels and found reduced expression of *Pomc* but increased methylation of *Pomc*gene in rats treated with alcohol on postnatal, juvenile or prepubertal period but not after pubertal period. These results identify a critical period for alcohol programming of the stress regulatory gene during the developmental period that causes stress hyperresponse and increases anxiety-like behaviors via epigenetic mechanisms.

Disclosures: G. Berger: None. **L. Chastain:** None. **O. Gangisetty:** None. **V. Murugan:** None. **M. Cabrera:** None. **D.K. Sarkar:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.12/C35

Topic: A.07. Developmental Disorders

Title: Cranial nerve abnormalities in fetal alcohol spectrum disorders

Authors: *N. K. BAER[1], B. M. BJORKE[2]
[2]Biol. Dept., [1]Carleton Col., Northfield, MN

Abstract: Prenatal alcohol exposure is the leading preventable cause of neurodevelopmental disorders. Those most effected display cognitive, structural, and motor defects and are diagnosed with fetal alcohol spectrum disorders (FASD). The teratogenic effects of alcohol on the avian embryo parallel those found in mammals including defects to cardiac function and alterations to neural crest migration influencing later craniofacial development. Previous research demonstrates that prenatal alcohol exposure significantly reduces Sonic hedgehog (Shh) signaling. A critical role of Shh is to act as a morphogen to inform the differentiation of motor neurons. Perturbation of Shh signaling during development may therefore explain the motor defects described in FASD. However, an examination of whether motor neuron development is altered following alcohol exposure is lacking.
We examined growth and guidance of the cranial nerves following early embryonic ethanol exposure in the avian model system. Chick eggs were exposed to 9 mM of ethanol, a physiologically relevant concentration that mimics persistent exposure to alcohol. Embryos were collected at time points following early nerve development and immunolabeled against beta-tubulin. The growth and guidance of the oculomotor and facial nerves were compared to PBS-injected and no-injection controls. Preliminary findings suggest a reduction in cranial nerve fiber density following ethanol exposure, which may indicate a decrease in the number of motor neurons. Subsequent research will focus on quantifying this reduction in motor neuron density and count.

Disclosures: N.K. Baer: None. **B.M. Bjorke:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.13/C36

Topic: A.07. Developmental Disorders

Support: UBACYT 20020130100258BA
UBACYT 20020130300033BA
PIP CONICET 00269

Title: Perinatal exposure to low doses of ethanol induces changes in cerebral areas analyzed at early postnatal days, which could be involved in characteristic adult behaviour

Authors: *H. A. BRUSCO, N. M. VILLALBA, C. MADARNAS, L. A. NOVAK, D. B. SORIANO, L. R. CALTANA, V. N. SANCHEZ
IBCN (UBA-CONICET) Facultad De Medicina UBA, Buenos Aires, Argentina

Abstract: Different animal models have been used to analyze the effect of ethanol (EtOH) during brain development and its consequences in adulthood. One of the most characteristic effects of *in utero* EtOH exposure is infant locomotor hyperactivity. However, studies on adult rats prenatally exposed to EtOH have rendered controversial results. Some authors have reported an increase in locomotor activity, while others have found no hyperactivity. In addition, previous studies found that adolescent mice and infant rats exhibit EtOH-induced locomotor activation. In view of these contrasting results, the aim of this work was to analyze adult behavior in CD1 mice perinatally exposed to low doses of EtOH (PEE) during gestation and lactation, and correlating it with morphological changes observed in their early postnatal brain. Primiparous CD1 female mice were exposed to EtOH 6%v/v intake for four weeks previous to mating. Pregnant mice drank EtOH 6%v/v during pregnancy and lactation. At the end of lactation, EtOH was eliminated and male pups were fed with food and water *ad libitum*. At P0 (postnatal day 0) and P17 pups were fixed and brain sections were stained. Morphometric parameters and nuclear characteristics were analyzed in hippocampus, cerebral premotor cortex and callosum. At P60, open field test were performed and locomotor activity, latency, time spent in periphery, time spent in central square and travelled distance were analyzed. In this PEE model, no differences were observed in weight gain in pregnant mice and in the number of offspring compared to the control group. Female mice consumed 0.261±0.08 ml EtOH/g/day, and yielded a BEC (blood EtOH concentration) of 73.29±8.69 mg/dl at the end of lactation. In PEE pups, BEC at P17 was 155.09±28.25 mg/dl and 101.56±5.21mg/dl at P21. There was a reduction of CA1 hippocampal area thickness in PEE pups at both P0 and P17; while a reduction of cerebral premotor cortex and the callosum thickness was found at P17. No morphological changes in nuclei were found. In adult PEE mice, behavioral estudies showed an increase in latency and a decrease in distance travelled compared to control animals. These results could be related with the alterations found in the studied brain areas.

Disclosures: H.A. Brusco: None. **N.M. Villalba:** None. **C. Madarnas:** None. **L.A. Novak:** None. **D.B. Soriano:** None. **L.R. Caltana:** None. **V.N. Sanchez:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.14/C37

Topic: A.07. Developmental Disorders

Support: NIH/NIGMS COBRE: The Delaware Center for Neuroscience Research Grant 1P20GM103653-01A1 to AYK
UD Summer Scholars Award to ECS
UD OGPE University Doctoral Fellowship to ZHG
Private Anonymous Gift to AYK

Title: Single-day binge early postnatal alcohol exposure causes region-specific patterns of short- and long-term damage in prefrontal-thalamic circuitry of rat

Authors: *Z. GURSKY, E. C. SPILLMAN, A. Y. KLINTSOVA
Dept. of Psychological & Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Fetal alcohol spectrum disorders constitute significant public health concern. Both human and animal studies link severity of prenatal alcohol-related brain damage to the timing and dose of alcohol to which the fetus is exposed. Previous findings in our lab indicate that behaviors dependent on mPFC - but not OFC - are impaired in a rodent model of human third trimester alcohol exposure (AE). The current study examined the impact of a single-day early postnatal binge AE on cell death and cell number in medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and the thalamic nucleus required for mPFC-hippocampal interactions (reuniens, Re). To test the hypothesis that AE restricted to postnatal day (PD) 7 selectively damages Re and mPFC, but not OFC, male and female Long Evans rat pups were either administered 5.25 g/kg/day of ethanol via intragastric intubation (AE group), intubated without liquid (sham-intubated, SI), or left undisturbed (suckle control, SC). Brain tissue was fixed and extracted on either PD7 (12 hours after experimental manipulation), PD11, or PD72. Brains were serially sectioned coronally at 40µm and sections were stained with cresyl violet. Unbiased stereological estimation of apoptotic cell number (PD7), total cell number (PD11, PD72), and volume (PD7, PD11, PD72) were performed for Re, mPFC, and OFC in each animal. All 3 regions displayed a significant 10-to-20-fold increase in apoptosis in AE animals on PD7, while levels of apoptosis in both SI and SC groups were very low and did not differ from each other. There was a main effect of postnatal treatment (but not age nor a significant interaction between factors) on cell number in Re, indicating that AE animals showed cell loss at both the PD11 and PD72 timepoints. A significant interaction between postnatal treatment and age was observed for mPFC cell number, due to a loss of cells at the PD11 timepoint in AE animals compared to both SI and SC, but no differences between treatments at PD72. In contrast, no significant differences were detected in OFC due to postnatal treatment, but an increase in cell number on PD72 relative to PD11. These data indicate that Re, mPFC, and OFC are differentially vulnerable to AE on PD7. While all 3 regions display increased cell death in response to alcohol on PD7, Re cell loss is present within 4 days from the insult and persists into adulthood, while mPFC cell deficits which are present short-term do not persist into adulthood, and OFC appears to be unaffected at PD11 or 72. The findings add to previous research presented by our lab indicating that PD4-9 AE targets Re within thalamus and selectively impairs mPFC-dependent behaviors among PFC-dependent behaviors.

Disclosures: Z. Gursky: None. **E.C. Spillman:** None. **A.Y. Klintsova:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.15/C38

Topic: A.07. Developmental Disorders

Support: NSF DGE-1745038
NIH R01 MH107515-01A1

Title: Polygenic contributions of general transcription factors, Gtf2i and Gtf2ird1, in Williams Beuren syndrome critical region to cognitive phenotypes

Authors: *N. D. KOPP[1], J. D. DOUGHERTY[2]
[2]Genet., [1]Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Williams Beuren syndrome (WS) is a neurodevelopmental disorder caused by a deletion of 26 genes on chromosome 7q11.23. Hemizygosity of these 26 genes results in a constellation of phenotypes including cardiovascular abnormalities, craniofacial dysmorphology, a unique cognitive profile, and gregarious personality. Human and mouse studies have implicated two transcription factors in the cognitive and social phenotypes, *Gtf2i* and *Gtf2ird1*. While single gene knock out studies in mice suggest that both of these genes individually contribute to social and cognitive phenotypes, we do not know if these paralogous transcription factors have additive effects or synergistic effects on behaviors. Further, we do not know how much of the phenotype caused by hemizygosity of the 26 genes can be explained by haploinsufficiency of *Gtf2i* and *Gtf2ird1*. CRISPR/Cas9 was used to generate mice lines that are haploinsufficient for either *Gtf2i* or *Gtf2ird1*. Crossing the two single haploinsufficient mouse lines allows us to compare the double haploinsufficient animals to single haploinsufficient and wild type littermates, so we can test single gene, additive, or epistatic genetic models. We tested these mouse lines in a battery of battery of motor, cognitive, and social behaviors in mice. Experimenters were blinded to genotype and for each task we aimed to test 15-24 animals per genotype and included both males and females. Behaviors such as activity levels and time spent in the center of an arena show additive effects; pre-pulse inhibition, contextual and cued fear show single gene effects; and balance and marble burying deficits are caused by an interaction between the two genes. Given the evidence for different genetic models, we test if haploinsufficiency of these two genes is sufficient to replicate the phenotypes in mice that lack all 26 genes typically deleted in WS. We cross a mouse line that is haploinsufficient for both *Gtf2i* and *Gtf2ird1* to a mouse line that is hemizygous for the genes deleted in WS, the complete deletion mouse (CD). We test the offspring of this cross on the same battery of behaviors. We see that the CD mice have a more severe phenotype than mice that are haploinsufficient for *Gtf2i* and *Gtf2ird1*, suggesting that there are contributions from other genes in the region to behavioral

phenotypes in mice. These studies provide evidence that *Gtf2i* and *Gtf2ird1* act additively as well as interact to affect behaviors. Further, these two genes alone are not sufficient to replicate the phenotype caused by hemizygosity of all the genes typically deleted in WS.

Disclosures: N.D. Kopp: None. **J.D. Dougherty:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.16/D1

Topic: A.07. Developmental Disorders

Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
Conselho Nacional de Desenvolvimento Científico e Tecnológico
Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro
Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos
Fundação de Amparo à Pesquisa do Estado de São Paulo
Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro

Title: Late neurological consequences of early-life Zika virus infection in mice

Authors: *P. DA SILVA FROST[1], I. NEM DE OLIVEIRA SOUZA[2], J. V. FRANÇA[3], J. NASCIMENTO-VIANNA[4], R. L. S. NERIS[5], L. FREITAS[8], D. J. L. L. PINHEIRO[9], C. O. NOGUEIRA[6], G. A. NEVES[11], L. CHIMELLI[12], F. G. DE FELICE[13], É. A. CAVALHEIRO[10], S. T. FERREIRA[14], A. THOMPSON DA POIAN[4], C. P. FIGUEIREDO[4], I. ASSUNÇÃO-MIRANDA[6], J. R. CLARKE[7]
[1]UFRJ, Rio De Janeiro, Brazil; [2]Fac. of Pharm., Federal Univ. of Rio De Janeiro, Rio De Janeiro, Brazil; [3]Inst. of Biomed. Sci., Federal Univ. of Rio De Janeiro, Rio De Janeiro, RJ, Brazil; [4]Federal Univ. of Rio De Janeiro, Rio De Janeiro, Brazil; [5]Inst. of Microbiology Paulo de Goes, Federal Univ. of Rio De Janeiro, Rio de Janeiro, RJ, Brazil; [6]Federal Univ. of Rio De Janeiro, Rio De Janeiro, RJ, Brazil; [7]Sch. of Pharm., Federal Univ. of Rio De Janeiro, Rio De Janeiro, Brazil; [8]Dept. of Neurol. and Neurosurgery,, Escola Paulista de Medicina, Federal Univ. of São Paulo,, São Paulo, SP, Brazil; [9]Dept. of Neurol. and Neurosurg., Escola Paulista de Medicina, Federal Univ. of São Paulo, São Paulo, SP, Brazil; [10]Dept. of Neurol. and Neurosurg., Escola Paulista de Medicina, Federal Univ. of São Paulo, São Paulo, Brazil; [11]Farmacologia, Univ. Federal do Rio De Janeiro, Rio De Janeiro, Brazil; [12]Lab. of Neuropathology, State Inst. of Brain Paulo Niemeyer, Rio De Janeiro, Brazil; [13]Fed Univ. Rio De Janeiro, Rio De Janeiro, Brazil; [14]Fed. Univ. Rio De Janeiro, Rio De Janeiro, Brazil

Abstract: A causal relationship has been established between congenital Zika virus (ZIKV) exposure and microcephaly and other neurological disorders. However, long-term consequences

of perinatal infection are largely unknown. Herein, we evaluated acute and late neuropathological and behavioral consequences of ZIKV infection in neonatal wild-type mice. ZIKV showed brain tropism, causing post-natal microcephaly and several behavioral deficits in adulthood. During the acute phase of infection, mice developed frequent epileptic seizures, which were consistently reduced by TNF-α neutralization. Although adult animals recovered from spontaneous seizures, they were significantly more susceptible to chemically-induced crises. ZIKV replication persisted in brains of adult mice, which exhibited marked brain necrosis and calcifications. Altogether, the results reveal the risk for the development of late neuropathological and behavioral complications caused by congenital or neonatal ZIKV exposure, and suggest the early inhibition of TNF-α-mediated neuroinflammation as a potential therapeutic strategy to prevent long-term neurological sequelae in ZIKV-infected infants.

Disclosures: P. Da Silva Frost: None. **I. Nem De Oliveira Souza:** None. **J. V. França:** None. **J. Nascimento-Vianna:** None. **R. L. S. Neris:** None. **L. Freitas:** None. **D. J. L. L. Pinheiro:** None. **C. O. Nogueira:** None. **G.A. Neves:** None. **L. Chimelli:** None. **F.G. De Felice:** None. **É. A. Cavalheiro:** None. **S.T. Ferreira:** None. **A. Thompson Da Poian:** None. **C.P. Figueiredo:** None. **I. Assunção-Miranda:** None. **J.R. Clarke:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.17/D2

Topic: A.07. Developmental Disorders

Support: Fonds de Recherche du Quebec - Santé (FRQ-S)
Foundation of Stars

Title: Chorioamnionitis induced by group B streptococcus serotype III: Intrauterine growth retardation and motor impairments in male rats

Authors: *M.-J. ALLARD[1], M.-E. BROCHU[2], J. BERGERON[2], M. SEGURA[3], G. SEBIRE[1,2]
[1]McGill Univ., Montreal, QC, Canada; [2]Univ. de Sherbrooke, Sherbrooke, QC, Canada; [3]Univ. de Montréal, Saint-Hyacinthe, QC, Canada

Abstract: INTRODUCTION: Chorioamnionitis is a polymicrobial infection - most often due to ascending genital bacteria - characterized by acute maternofetal inflammation. Chorioamnionitis is a major risk factor for intrauterine growth retardation (IUGR), associated with premature birth and brain injuries, which may result in cerebral palsy and other long-term neurologic deficits. However, the causal link between chorioamnionitis and IUGR has not been demonstrated yet. The pathogen(s) involved in this sequence of perinatal morbidities remain unknown. Common isolates in women with chorioamnionitis include group B Streptococcus (GBS) serotypes Ia and

III. Serotype III GBS is considered more virulent than serotype Ia, and is associated with worse clinical outcomes. We aimed to compare the impact of end-gestational exposure to serotype Ia and III, considering GBS serotype-specific virulence asset. METHODS: Dams were injected every 12 h from gestational day 19 to 22 with saline, inactivated GBSIa or GBSIII, as previously described (Bergeron JD et al., 2013). The open field apparatus was used to evaluate spontaneous locomotion, exploratory behavior and thigmotaxis in a novel environment. RESULTS: End-gestational exposure to GBSIa and GBSIII and subsequent chorioamnionitis impacted negatively the maternal weight gain, without leading to increased mortality rate in the progeny. No premature delivery was noticed in any group, *i.e.* all dams gave birth naturally on G23/P0 GBSIII - but not GBSIa - induced chorioamnionitis impacted negatively the pups' weight at birth, suggesting an IUGR, and this growth retardation was still present at P40. At P25, GBSIII-exposed males - but not females - displayed an impaired motor behavior in the open field apparatus, but no anxiety-like behavior or impaired exploratory behavior was observed. GBSIII-exposed males - but not females - had a thinner primary motor cortex than controls at P40, which was correlating with the total distance travelled in the open field. CONCLUSIONS: Our results showed for the first time that end-gestational exposure to GBS lead to serotype-specific and sex-specific neuromotor impairments. These results validate the pertinence to further investigate whether GBSIII triggers a differentiated inflammatory response from GBSIa, and subsequently leads to worst neurodevelopmental impacts associated with motor and/or cognitive deficits.

Disclosures: M. Brochu: None. **J. Bergeron:** None. **M. Segura:** None. **G. Sebire:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.18/D3

Topic: A.07. Developmental Disorders

Title: Behavioral analysis of the progeny of rats exposed to the toxoplasma gondii extract

Authors: *E. ROMERO NUÑEZ, B. PINEDA[1], A. JIMENEZ-ANGUIANO[2], S. MUÑIZ HERNÁNDEZ[3], D. F. GONZÁLEZ ESQUIVEL[1], C. RÍOS[1], V. PÉREZ DE LA CRUZ[1]
[1]Inst. Nacional de Neurología y Neurocirugía, Ciudad de México, Mexico; [2]Univ. Autonoma Metropolitana-Iztapalapa, Mexico City, Mexico; [3]Inst. Nacional de Cancerología, Ciudad de México, Mexico

Abstract: Toxoplasmosis is a parasitic infection caused by the protozoan *Toxoplasma gondii* whose prevalence is estimated as 30% of the world population. Generally, the infection is considered asymptomatic, although recently it has been associated with some behavioral alterations in the host. In the case of maternal infection, *T. gondii* has been recognized as a risk factor for abnormal brain development in the fetus because it can invade the central nervous

system, but even in the absence of perinatal transmission, infection during the pregnancy could play an important role in the neurological development of the offspring. The aim of this work is to evaluate behavioral changes in the progeny of rats immunized with *T. gondii* antigens. Female wistar rats were injected with the *T. gondii* lysate or PBS three times (once per week) prior to gestation. In the progeny was evaluated Memory and learning, locomotor activity in the open field and social interaction at 60 postnatal days. In the locomotor activity test, the progeny of mothers previously immunized with the *T. gondii* lysate showed a decrease (26%) in the total distance traveled, compared with the control group. In the object recognition test, the progeny of mothers previously immunized with the *T. gondii* lysate showed a lower preference (67%) for the novel object, compared to the control group. Regarding the social interaction test, the progeny of mothers previously immunized with the *T. gondii* lysate showed less interest (58%) in interacting with another rat either known or unknown, compared to the control group showing greater preference for interacting with the novel rat. These results suggest that the progeny of mothers previously immunized with the *T. gondii* lysate presents behavioral and social impairment possibly as a result of immune maternal system alteration by *T. gondii* antigens.

Disclosures: E. ROMERO Nuñez: None. **B. Pineda:** None. **A. Jimenez-Anguiano:** None. **S. Muñiz Hernández:** None. **D.F. González Esquivel:** None. **C. Ríos:** None. **V. Pérez de la Cruz:** None.

Poster

641. Developmental Disorders: Animal Models of Neurodevelopmental Disease III

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 641.19/D4

Topic: A.07. Developmental Disorders

Support: Canadian Institute for Health Research (CIHR)
Brain Canada (BC)
Ontario Brain Institute (OBI)
Kids Brain Health Network (KBHN, formerly NeuroDevNet)

Title: Subtle effects of chronic glycogen synthase kinase 3β inhibition on the behaviour and neuroanatomy of five mouse models of autism

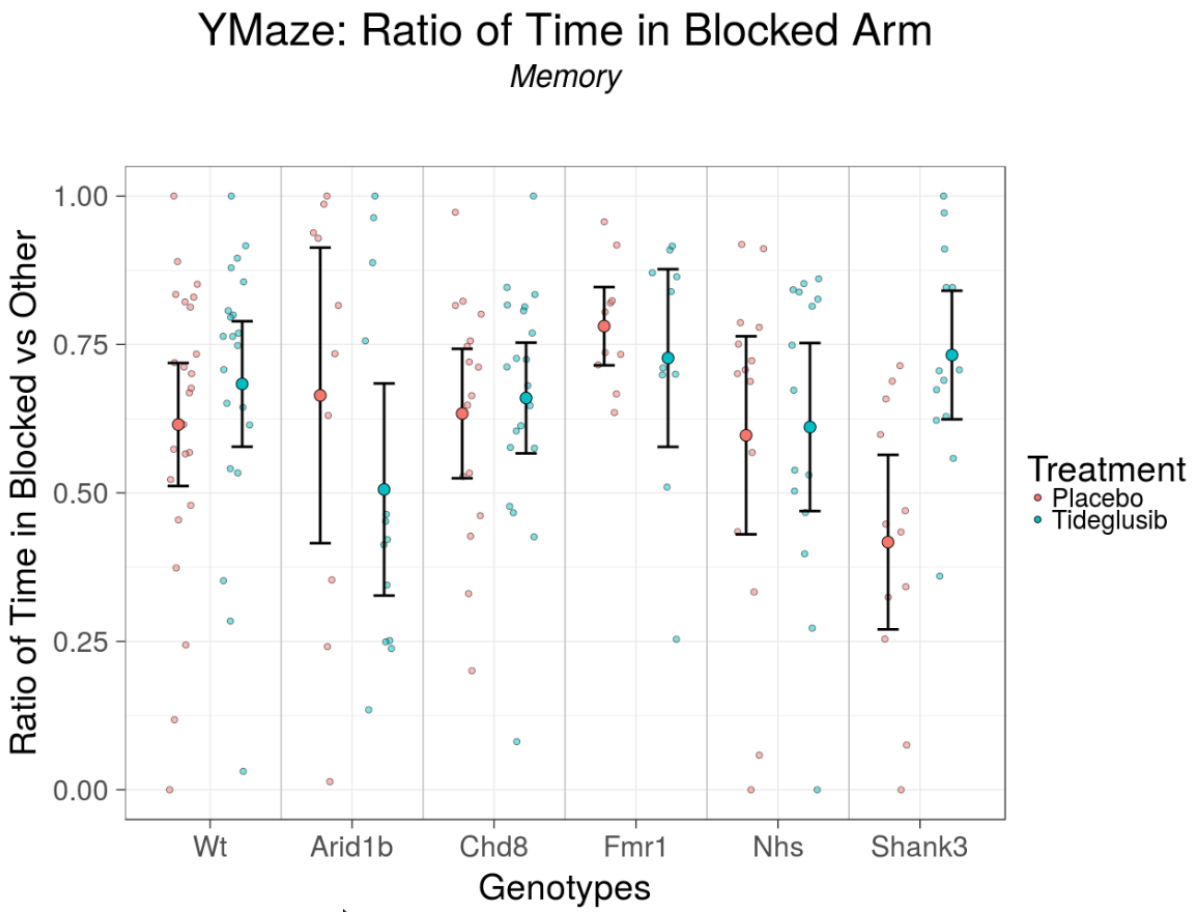
Authors: *Z. BUCHWALD[1], A. KINMAN[1], T. CHIEN[1], K. EASSON[1], J. ELLEGOOD[1], J. FOSTER[2], E. ANAGNOSTOU[3], J. LERCH[1]
[1]Mouse Imaging Center, Hosp. For Sick Children, Toronto, ON, Canada; [2]Psychiatry & Behav Neurosci, McMaster Univ., Hamilton, ON, Canada; [3]Holland Bloorview Kids Rehabil. Hosp., Toronto, ON, Canada

Abstract: Tideglusib, a glycogen synthase kinase β inhibitor, is predicted to alleviate autism-related symptoms, increase neurogenesis and memory formation (Guo et al.2012, Hermida et al. 2017). In this study, we treated five different autism mouse models with Tideglusib to characterize the effects on the behaviour and neuranatomy of the mice. The five mouse models chosen represent either single-gene disorders related to autism (like Fragile X Syndrome) or common mutations present in the autism population: Fmr1 and NHS hemizygous knockout models, the CHD8 and Arid1b heterozygous deletion models, and the Shank3 homozygous knockout model.

Mice were administered 5mg/kg I.P. Tideglusib five days a week, for four weeks, starting at 5 weeks of age. On the final week of treatment, a battery of behavioural assessments were conducted to assess sociability, memory, anxiety, and hyperactivity. Magnetic resonance imaging (MRI) was used to assess the effects of treatment on neuroanatomy at three *in vivo* and one *ex vivo* timepoints.

A significant effect of Tideglusib treatment was found in the behaviour of the Shank3 mouse model, with treatment normalizing a memory deficit in Ymaze but exacerbating O-maze hyperactivity and decreasing anxiety past wildtype levels (the figure shows mean and 95% confidence intervals for all strains on the Ymaze memory test). No treatment effect was found in the *ex vivo* neuroanatomy of any of the mouse models, nor on the behaviour of any of the other strains, although some trends were seen in the Chd8 and NHS mice.

These results indicate that though Tideglusib is beneficial for the memory deficits of the Shank3 mouse model, it may have harmful side effects in other behaviours, and therefore may not be a suitable treatment for humans. Tideglusib also showed no effect on the neuroanatomy, although comparison to baseline and the longitudinal effect of Tideglusib on structural anatomy remains to be determined. In conclusion, the effect of chronic treatment with Tideglusib may be more subtle than originally anticipated.



Disclosures: Z. Buchwald: None. **A. Kinman:** None. **T. Chien:** None. **K. Easson:** None. **J. Ellegood:** None. **J. Foster:** None. **E. Anagnostou:** None. **J. Lerch:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.01/D5

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

Support: NIH Grant EY015788
NIH Grant EY023105
NIH Grant EY025968
NIH Grant P30 EY000785
NIH Grant R01 EY015788

Title: Origin and function of directionality in spontaneous retinal waves

Authors: *X. GE, A. GRIBIZIS, M. C. CRAIR
Neurosci., Yale Univ., New Haven, CT

Abstract: Before the onset of visual experience, spontaneous retinal waves are the main source of activity in the developing superior colliculus (SC), thalamus and primary visual cortex in the mammalian visual system. Genetic and pharmacological manipulations of this spontaneous retinal activity suggest a causal link between retinal waves and circuit refinement. Previous studies found that Stage II (around the first week after birth in mice) spontaneous waves exhibit a strong directional bias. However, it remains unclear how this bias emerges, whether it changes over development and whether this spatiotemporal feature of spontaneous waves is critical for circuit refinement and the development of functional circuit properties. Here, we describe experiments that investigate the role and origin of spontaneous wave directionality during visual system development. We used wide-field Ca^{2+} imaging of retinal ganglion cell (RGC) projections in the SC *in vivo* and optogenetic or light stimulation of the retina to examine spontaneous and stimulus induced wave direction bias. We observe that the directional bias emerges at the end of Stage II (~P8) waves and vanishes before the time of eye opening (~P12). The biased direction (temporal to nasal) is consistent between P8 and P12. The averaged wave propagation direction distribution resembles the optic flow pattern in the retina generated by forward motion. To understand the origin of wave directional bias *in vivo*, we used selective optogenetic stimulation of starburst amacrine cells (SACs), or light stimulation after the onset of light response (~P10), to initiate waves at various locations in the retina. Our experiments suggest that starting from around P10, stimulated retinal waves propagate in a direction consistent with intrinsic waves, regardless of their nucleating sites. This suggests a biased retinal circuit that favors the propagation of waves in a specific direction on the retina. In addition, we show that pharmacological blockade of inhibition *in vivo* diminished wave directional bias. This result suggests that inhibition plays an especially important role in establishing the strong directional bias of spontaneous retinal waves. In summary, these results suggest a specific developmental stage in which spontaneous retinal waves exhibit a strong directional bias, and that this bias is a result of intrinsic asymmetry in the retinal circuit. This bias could potentially affect visual circuit refinement in the retina and other parts of the developing visual system.

Disclosures: X. Ge: None. **A. Gribizis:** None. **M.C. Crair:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.02/D6

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

Support: BFU2015-64432-R

ERC-2014-CoG-647012

Title: Spontaneous thalamic waves regulate cortico-thalamic innervation in the visual system

Authors: *V. MORENO-JUAN, G. LOPEZ-BENDITO
Inst. de Neurociencias UMH/CSIC, San Juan de Alicante, Spain

Abstract: Understanding how do cortical areas acquire their functional identity is a central question that has been studied for many years. To determine how the brain adapts to the sensory lost might help to better decipher the role of extrinsic and intrinsic mechanisms in cortical development. We have recently demonstrated an unpredicted role of the prenatal thalamus in shaping cortical territories after input deprivation, which depends on the propagation of spontaneous calcium waves across the different thalamic sensory nuclei (Moreno-Juan et al., 2017). Now, we have evidences that suggest that spontaneous thalamic activity is crucial for the correct development of the corticothalamic projections in the visual system. Here we have shown that consistent to what was published before, in embryonically bienucleated (embBE) mice, corticothalamic axons (CTAs) prematurely invade the dorsal lateral geniculate nucleus (dLGN) at P4 and thus suggesting that retinal axons have a pivotal role in the control of the CTAs segregation and synapses maturation in the dLGN. However, it is still possible that the role of the retinal axons in controlling the innervation of the CTAs is indirect by modulating the thalamic intrinsic activity. Indeed, the thalamic calcium waves in the dLGN persist in absence of retinal input and moreover, their frequency is increased. So it is possible that CTAs invasion is controlled by thalamic calcium waves rather than purely by the presence or absence of retinal axons. We have performed several experiments in retinal or thalamic silenced mice using specific drug injections or transgenic modified animals in order to better characterize the mechanisms that control the corticothalamic innervation in the visual thalamus. Moreover, it is possible that thalamic spontaneous activity controls the expression pattern of genes in the dLGN that might be important for CTA targeting. We have performed a microarray assay in which the dLGN genetic profile of the embBE mice was analyzed. Thus, we have a powerful suitable dataset in which to look for specific activity-dependent genes involved in controlling the entrance of the CTAs. Altogether these results contribute to elucidate the role of the thalamus in cortical development.

Disclosures: V. Moreno-Juan: None. **G. Lopez-bendito:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.03/D7

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

Support: ERC-2014-CoG-647012
BFU2015-64432-R
PROMETEO/2017/149

Title: Embryonic thalamic calcium waves control barrel map formation through the developmental regulation of cortical excitability

Authors: N. ANTÓN-BOLAÑOS[1], A. SEMPERE-FERRÀNDEZ[1], F. MARTINI[1], L. PÉREZ SAIZ[1], H. GEZELIUS[1,2], A. FILIPCHUK[1,3], A. ESPINOSA[1], M. A. VALDEOLMILLOS[1], *G. LOPEZ-BENDITO[1]
[1]Developmental Neurobio. Unit, Inst. De Neurociencias, Alicante, Spain; [2]Sci. for Life Lab., Solna, Sweden; [3]UNIC, CNRS, Gif-Sur-Yvette, Paris, France

Abstract: Sensory periphery systems are represented in cortical primary sensory areas of the brain, organized in anatomical and functional maps. For instance, the whisker pad representation in the barrel field of S1 in rodents. Several intrinsic and extrinsic factors have been proposed to shape sensory maps during early development. Thalamic spontaneous calcium waves which propagate from the thalamus to the cortex during perinatal stages, might influence sensory map development. To test this possibility, we developed a mouse model in which the pattern of spontaneous thalamic activity is modified due to the specific abolishment of the calcium waves in this structure. In this mouse (Th^{kir}), thalamic neurons are hyperpolarized due to the overexpression of Kir2.1. *Ex vivo* calcium imaging in postnatal acute slices showed that at P2-P3, VPM stimulation generates a cortical propagating activity in the Th^{Kir}, in contrast to the pre-columnar restricted domains generated in control animals before barrel formation. Moreover, our data shows that the cortex of Th^{kir}mice remains hyper-reactive throughout the first postnatal week, as indicated by the higher frequency of spontaneous cortical activity in comparison with control mice. The change in this pattern of thalamic activity and therefore the cortical excitability lead to the complete lack of the somatosensory map representation in S1. Remarkably, thalamocortical axons (TCAs) reach their cortical target layer 4 but do not segregate in cortical barrel-like patches as observed in control mice, lacking their characteristic point-to-point refined organization. In sum, our results demonstrate a crucial role of the prenatal thalamic calcium waves in the acquisition of cortical sensory maps in the somatosensory system by the postnatal regulation of cortical excitability.

Disclosures: N. Antón-Bolaños: None. **A. Sempere-Ferràndez:** None. **F. Martini:** None. **L. Pérez Saiz:** None. **H. Gezelius:** None. **A. Filipchuk:** None. **A. Espinosa:** None. **M.A. Valdeolmillos:** None. **G. Lopez-Bendito:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.04/D8

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

Support: University Grants Commission, India
Department of Biotechnology, DST, India
TIFR-DAE intramural funds

Title: LDB1 is required for the early development of the dorsal telencephalon and the thalamus

Authors: V. KINARE[1], S. PAL[2], *S. P. TOLE[3]
[1]Sophia Col. for Women, Mumbai-400, 005, India; [2]Tata Inst. of Fundamental Res., Mumbai, India; [3]Tata Inst. of Fundamental Res., Mumbai-400, 005, India

Abstract: LDB1 is a protein cofactor that participates in several multiprotein complexes with transcription factors that regulate forebrain development. Since Ldb1 null mutants display early embryonic lethality, we used a conditional knockout strategy to examine the role of LDB1 in early forebrain development, using multiple Cre lines. Loss of Ldb1 using Foxg1Cre caused a disruption of midline boundary structures in the dorsal telencephalon. While this Cre line gave the expected pattern of recombination of the floxed Ldb1 locus, unexpectedly, standard Cre lines that act from E10.5 (Emx1Cre) and E11.5 (NesCre) did not show efficient or complete recombination in the dorsal telencephalon by E12.5. Intriguingly, this effect was specific to the Ldb1 floxed allele, while three other lines including floxed Ai9 and mTmG reporters, and a floxed Lhx2 line, each displayed the expected patterns of recombination. Furthermore, the incomplete recombination of the floxed Ldb1 locus using NesCre was limited to the dorsal telencephalon, while the ventral telencephalon and the diencephalon displayed the expected loss of Ldb1. This permitted us to examine the requirement for LDB1 in the development of the thalamus. We report that the somatosensory VB nucleus is profoundly shrunken upon loss of LDB1. Our findings highlight the unusual nature of the Ldb1 locus in terms of recombination efficiency, and also report a novel role for LDB1 during the development of the thalamus.

Disclosures: V. Kinare: None. **S. Pal:** None. **S.P. Tole:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.05/D9

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

Support: Department of Biotechnology(DBT), India
TIFR-DAE

Title: Genetic mechanisms in early cortical progenitors control thalamocortical innervation

Authors: *S. PAL, G. GODBOLE, T. PRAMANIK, S. TOLE
Dept. of Biol. Sci., Tata Inst. of Fundamental Res., Mumbai, India

Abstract: Sensory information from the periphery is presented to the cerebral cortex in a highly ordered manner, providing a topographic representation of the external world. In the mouse, sensory information from the whiskers is spatially represented via maps in the brainstem and thalamus from where it enters the somatosensory cortex to form whisker-specific “barrels.” We have discovered a genetic tool that allows us to examine how the innervation of the cortex by thalamocortical afferents is regulated. Using a cortex specific and progenitor-specific conditional mutant of transcription factor Lhx2, we discovered that the cortical barrels do not form. Therefore, the Lhx2 deficient cortex causes a non-cell-autonomous disruption of incoming thalamocortical innervation. This disruption is seen at very early stages, suggesting mechanisms in operation that have not previously been reported. The cortex-specific Lhx2 conditional mutant offers new insights into the problem of thalamocortical guidance.

Disclosures: S. Pal: None. **G. Godbole:** None. **T. Pramanik:** None. **S. Tole:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.06/D10

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

Support: 5R01EY011488-19

Title: Development of coherent orientation selective responses to monocular and binocular stimuli in ferret visual cortex

Authors: *J. T.-Y. CHANG, D. E. WHITNEY, D. FITZPATRICK
Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: In the mammalian primary visual cortex, neurons form networks that are characterized by selectivity to visual features such as orientation, a property known to emerge during early postnatal life. While orientation preferences for each eye are matched in the mature visual system, we recently demonstrated that at the onset of visual experience orientation tuning through the two eyes is initially mismatched at both the cellular and network-level, and only later becomes reconciled with exposure to a week of patterned visual experience. However, the process and factors that drive toward a coherent representation of orientation tuning remain poorly understood. For example, one possible outcome is a winner-take-all approach where the orientation preference of the dominant eye drives the remapping of orientation preference of the non-dominant eye.
Here we use longitudinal functional imaging of GCAMP6s over the first week of patterned visual experience to assess orientation selective responses to either the monocular or binocular presentation of drifting gratings. Surprisingly, we find that patterns of cellular and network level responses evoked by binocular stimulation are distinct from those of monocular stimulation at eye-opening, and not merely predicted as a simple weighted sum of monocular responses. Furthermore, we demonstrate that metrics of ocular dominance and reliability fail to predict the experience-dependent shifts in monocular orientation preferences. Indeed, most cortical neurons remain highly binocular during this developmental epoch, suggesting that the shift in orientation preferences cannot merely be accounted for by increases in monocularity or changes in ocular dominance. Instead, our imaging data show that responses evoked by binocular stimulation remain relatively stable over the first week of visual experience and monocular responses shift progressively to match the binocular response. Thus, we propose that a stable binocular response is the template for remapping monocular responses, and anchors the final representation of orientation tuning in primary visual cortex.

Disclosures: J.T. Chang: None. **D.E. Whitney:** None. **D. Fitzpatrick:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.07/D11

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

Support: NIH RO1 EY023871
NIH F31 EY027196

Title: V1 pyramidal neurons lose dendritic inhibition and somatic disinhibition across critical period closure

Authors: *C. E. YAEGER[1], D. L. RINGACH[2], J. T. TRACHTENBERG[1]
[1]Neurobio., [2]Neurobio. & Psychology, UCLA, Los Angeles, CA

Abstract: During development, long-lasting changes in neural circuitry are rapidly induced by sensory exposure. The mechanisms of sensory-dependent plasticity are not understood, nor is it known how plasticity rules shift with maturation. Here we show a microcircuit unique to the developmental critical period in mouse primary visual cortex, in which behavioral state and inhibition converge to alter compartmentalized dendritic responses and somatic excitability. Using 2-photon microscopy to measure GCaMP6 fluorescence in awake mice viewing natural movie scenes, we find that sister dendrites of L2/3 pyramidal cells are strongly decorrelated during movement in young mice but not in adults. Locomotion also strongly activates a population of interneurons that innervate pyramidal cell dendrites-- somatostatin-expressing (SST) interneurons-- but only prior to critical period closure. Whole-cell recordings in slice indicate that SST cells lose cholinergic responsivity across developmental time points. These changes in SST-mediated inhibition also affect parvalbumin-expressing (PV) interneurons and their primary target, pyramidal cell somas. During the critical period, PV interneurons are inhibited during locomotion and cholinergic release, subsequently removing inhibitory drive onto pyramidal cell somas. Optogenetic stimulation of SST cells in adult cortex restores both branch-specific dendritic responses and somatic disinhibition in pyramidal neurons. Thus, cholinergic sensitivity of SST cells affects dendritic and somatic excitatory processing through direct and indirect means. We propose that the age-dependent inversion of inhibition along the somato-dendritic axis alters local plasticity rules and contributes to the closure of critical periods.

Disclosures: C.E. Yaeger: None. **D.L. Ringach:** None. **J.T. Trachtenberg:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.08/D12

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

Support: NIH grant DC015137

Title: Modeling the development and binocular matching of orientation preferences of binocular neurons in layer 2/3 of V1

Authors: *X. XU[1], H. RIECKE[2]
[2]Engin. Sci. and Applied Mathematics, [1]Northwestern Univ., Evanston, IL

Abstract: Information about the world reaches the brain via multiple sensory information channels. This variety of inputs needs to be merged in a coherent fashion to provide meaningful information. The mouse visual system is an excellent model system to investigate such merging. At eye-opening (P13-P15) binocular cells in V1 have already developed significant orientation tuning, but the preferred orientations for input from the left and from the right eye typically differ significantly. With normal visual experience during a critical period (P19-P30) these orientations shift and eventually become well matched [1]. Recent experiments have shown that the binocular matching process, which is completely blocked by monocular deprivation spanning the entire critical period, can be rescued by environmental enrichment to the level seen in normal mice [2].

To gain insight into the matching process, we developed a computational model of a cortical cell in L2/3 that receives - via monocular cells in L4 - oriented inputs from the two eyes via synapses that exhibit voltage-based spike-timing dependent plasticity. Employing a monocular stage of development followed by a binocular one, our model captured the experimentally observed matching of the orientation preferences, the dependence of the matching process on the ocular dominance of the cell, and the inverse relationship between the resulting binocular orientation selectivity and the mismatch. Moreover, our model puts forward testable predictions regarding the interplay of ocular dominance, orientation selectivity, and the matching of preferred orientations. Two different routes of matching are predicted depending on the initial degree of the mismatch.

We expect that these results provide insight more generally into the development of systems that integrate inputs from multiple sources in order to generate normal neuronal functions.

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[2] Jared N Levine, Hui Chen, Yu Gu, and Jianhua Cang, "Environmental Enrichment Rescues Binocular Matching of Orientation Preference in the Mouse Visual Cortex.", J. Neuroscience 37 (2017), pp. 5822--5833.

Disclosures: X. Xu: None. **H. Riecke:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.09/D13

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

Support: NIDCD R01 014101
The Sandler Foundation
Hearing Research, Inc

The Klingenstein Foundation
The Coleman Memorial Foundation
T32 MH089920
NIH R01 MH081880

Title: Function of vasoactive intestinal peptide (VIP)-expressing interneurons in the developing auditory cortex

Authors: *J. HU[1], J. BIGELOW[3], R. J. MORRILL[2], J. L. RUBENSTEIN[5], A. R. HASENSTAUB[4]
[1]Dept. of Psychiatry, [2]Univ. of California, San Francisco, San Francisco, CA; [4]Otolaryngology / Ctr. for Integrative Neurosci., [3]UCSF, San Francisco, CA; [5]Nina Ireland Lab. Dev Neurobiol, Univ. of California San Francisco, San Francisco, CA

Abstract: In adult mice, distinct cortical interneuron subtypes uniquely process sensory information. However, their roles during postnatal development of the sensory cortex are poorly understood. Transcription factors direct the development and function of cortical interneurons in a subtype-specific fashion. Among these is *Coup-TF2 (Nr2f2)*, an orphan nuclear receptor whose expression is restricted to a few interneuron subtypes. We analyzed the effect of conditionally removing *Coup-TF2* in vasoactive intestinal peptide (VIP)-expressing interneurons during early postnatal development. We found a ~40% reduction in VIP+ interneuron density that first occurred at age P3 through cell death. We then examined the consequences of this reduction on sensory processing through extracellular *in vivo* recordings in the adult primary auditory cortex. We observed frequency tuning curves with smaller bandwidths and perturbed tonotopic map. These effects were associated with changes in layer-specific firing responses, altered spike waveform duration and response onset (peristimulus time histogram (PSTH)) in fast-spiking cells, and changes in post-stimulus firing (PSTH) in regular-spiking cells. Altogether, our data support a specific role in VIP+ interneurons during the development of circuits that process auditory stimuli.

Disclosures: J. Hu: None. **J. Bigelow:** None. **R.J. Morrill:** None. **J.L. Rubenstein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona. **A.R. Hasenstaub:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.10/D14

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

Support: NS 074972

Title: Developmental regulation of top-down inputs onto L1 neurons in the Primary Auditory Cortex

Authors: *L. A. IBRAHIM[1], N. YUSUF[1], R. MACHOLD[2], G. J. FISHELL[1]
[1]Dept. of Neurobio., Harvard Med. Sch., Boston, MA; [2]NYU Langone Med. Ctr. Neurosci. Inst., New York, NY

Abstract: Information processing in a sensory cortex is determined not only by 'bottom-up' sensory experience, but by feedback from higher cortical areas, modulation by subcortical systems, as well as cross-modal modulation by other sensory cortices. Many of these projections exist to create an internal representation that predicts the incoming stimuli to react faster and draw conclusions based on limited information. How this develops and is achieved in sensory cortices is not well understood. It is likely that L1 interneurons might play a role. They receive both strong cortico-cortical inputs from higher order cortices, as well as bottom up thalamic inputs, and their inhibitory nature puts them in a suitable position to modulate sensory processing. Our preliminary rabies data suggests that in the primary auditory cortex (A1), the thalamic inputs onto the 'neuron derived neurotrophic factor' (NDNF) interneurons, the largest subset of L1 interneurons, while decreasing during development, persist into adulthood. We hypothesize that this initially large bottom up sensory input might be important in establishing long rage top-down inputs onto L1 neurons and impart important functions to these neurons in sensory processing. Previous work in our laboratory has shown that Prox1, a homeobox transcription factor is required for the specification and integration of CGE (Caudal ganglionic eminence) derived interneurons. Whether this is also an important factor in establishing long range connectivity is still not known. Our preliminary data shows that removal of Prox1 affects connectivity of these interneurons; a decrease in local, long range as well as cholinergic inputs was observed. It is possible that this effect might be due to a broad role of Prox1 in maintaining CGE identity; hence, identifying specific molecules that are regulated by Prox1 action is important in determining the molecular basis of top-down input establishment in A1.

Disclosures: L.A. Ibrahim: None. **N. Yusuf:** None. **R. Machold:** None. **G.J. Fishell:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.11/D15

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

Support: NIH NIDCD R03 014017
NIH NIDCD R01 016063
Johnston Family Foundation

Title: Neural dynamics in the developing piriform cortex

Authors: *Z. ZHANG, D. C. COLLINS, J. X. MAIER
Neurobio. and Anat., Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Revealing the mystery of cortical development can help us understand how cortical circuits learn to process information. Previous work has focused on how cortical computations are shaped by sensory input during the critical period. However, recent work on the visual and somatosensory systems has shown that cortex learns to process information already in the absence of sensory input, during the pre-critical period. For example, before maturation of the retina, spontaneous retinal waves trigger 10 Hz spindle oscillations in the thalamo-cortical loop that drive initial patterning of visual cortex.In contrast, nothing is known about the development of piriform olfactory cortex—a 3-layer paleocortex that lacks thalamic relay and receives natural sensory input from birth. These odd features, in combination with an evolutionary history that is shared with neocortex, make piriform cortex a unique model for studying cortical development. Here, we ask whether the same activity patterns observed during development of neocortex are observed in piriform cortex. We recorded local field potential activity in the piriform cortex of urethane-anesthetized rats across development, from postnatal day 0 days to adulthood. Odor and clean air were presented for 5 s with 30-45 s intervals. Respiration was recorded with a pressure sensor.Our results show that immediately after birth, respiration drives 10 Hz odor-evoked spindle oscillations in piriform cortex. These oscillations increase in frequency during the first two weeks of life until they reach adult values of ~20 Hz. The transformation from spindle to beta oscillation is not gradual but occurs suddenly around 15 days of age. At the same time, spontaneous activity undergoes a dramatic increase in structure. These findings indicate that early developmental dynamics observed in piriform cortex activity are highly similar to those previously observed in neocortical sensory areas, despite major differences in circuits, systems and peripheral input. This suggests that the principles underlying cortical development are evolutionarily conserved, and that sensory cortical development is coordinated across the brain. Ongoing work focuses on characterizing spiking activity, as well as developmental activity patterns in awake rats.

Disclosures: Z. Zhang: None. **D.C. Collins:** None. **J.X. Maier:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.12/D16

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

Support: NIH grant 1F31 NS093790-01
NIH grant T32 NS0624443

NIH grant NEI 1R01EY027380

Title: The development of multisensory integration is influenced by network correlation and sensory experience

Authors: *T. L.-S. TRUSZKOWSKI[1], J. BLEIER[2], S. COHEN[2], C. D. AIZENMAN[1]
[1]Neurosci., [2]Brown Univ., Providence, RI

Abstract: The interaction of sensory information from multiple senses provides crucial information to the brain. Previously, we have used the Xenopus tadpole optic tectum to show that multisensory integration is sensitive to stimulus interval and shows inverse effectiveness. These are dependent on maturation of inhibition and NMDAR activation respectively. However, these studies raise the question of how single cell activity could give rise to behavior and how that process could be manipulated with experience. First, we investigated the interactions among cells in the optic tectum using in vivo calcium imaging. The optic tectum has a subset of cells that are highly correlated with a large number of other cells in response to both multisensory and unisensory stimuli. This may indicate the presence of a few highly connected cells in the optic tectum that may act as network influencers to coordinate multisensory responses across the tectum. Younger tadpoles have more of these highly correlated cells, suggesting that correlation decreases over development. This may indicate a mechanism by which a subset of cells provide sensory input that is processed differently by a variety of functional cell types. Our data provides novel insight into how cells process multisensory information as a functional group. Furthermore, we showed that temporally disparate multisensory experience changes the multisensory responses behaviorally and in single cells. In particular, single cell spike responses are shifted towards a conditioned temporal interval and tadpoles show increased behavioral responses to the conditioned interval. Together, these data provide a robust, multi-faceted assessment of the development of multisensory integration in the Xenopus tadpole.

Disclosures: T.L. Truszkowski: None. **J. Bleier:** None. **S. Cohen:** None. **C.D. Aizenman:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.13/D17

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

Support: Wellcome Investigator Award, grant number 204788/Z/16/Z, awarded to Martin Meyer

Title: Experience dependent development of prey capture performance in larval zebrafish

Authors: *K. LAGOGIANNIS, M. MEYER
King's Col. London, London, United Kingdom

Abstract: Hunting in larval zebrafish is an innate behaviour that emerges early during their development. These larvae rely on sensorimotor coordination in order to visually track down and capture moving prey. The developmental mechanisms that lead to the rapid emergence of such robust sensorumotor loops are not known. We have developed a behavioural tracking system that permits detailed analysis of hunting routines and are using this to examine the role of hunting experience in the development of hunting behaviour. Our data suggest that hunting success improves with prior experience while not affecting the probability of engaging in hunting behaviour. These findings provide a basis for probing how the reward associated with the consumption of prey and/or exposure to a natural sensory stimulus (prey) contribute to the development of visuomotor circuits optimized for hunting.

Disclosures: K. Lagogiannis: None. **M. Meyer:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.14/D18

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

Support: R01EY25670
R01EY16187
William Randolph Hearst Fellowship

Title: Multiple body maps in newborn macaques

Authors: *M. J. ARCARO, P. F. SCHADE, M. S. LIVINGSTONE
Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Like the visual and auditory systems, somatosensory and motor systems exhibit substantial postnatal plasticity. We previously reported that the entire visual system of neonatal macaques is organized into a series of retinotopic maps that we proposed act as a proto-organization for subsequent postnatal experience-dependent plasticity (Arcaro & Livingstone, 2017, eLife). Here we explored the organization of the neonatal somatosensory system.
We used fMRI of alert infant monkeys to measure responses to tactile stimulation starting as early as 11 days through two years of age. To map representations of the body, we applied tactile stimulation to the face, hands, legs, and body. To map representations of individual fingers, we applied tactile stimulation to each digit.
Even at the earliest timepoint measured, 11 days, somatosensory and motor regions already

comprised several topographically organized representations of the body. Body maps were identified within primary and secondary somatosensory cortex (SI & SII), supplementary motor area (SMA), primary motor (M1), pre-motor (F5), the insula, the putamen, the globus pallidus, and the ventral posterior nucleus of the thalamus. An additional representation of the face was found in posterior parietal cortex within anterior parts of the ventral intraparietal area (VIP). Representations of individual fingers could be mapped in SI and SII. The extent and organization of these body maps were comparable to the organization found in juveniles and older monkeys. We propose that the body-map organizations of the somatosensory and motor systems are present at birth and are the result of self-organizing mechanisms. We speculate that this early architecture provides a scaffolding that supports and constrains the development of neural circuits promoting complex movements and fine tactile abilities.

Disclosures: M.J. Arcaro: None. **P.F. Schade:** None. **M.S. Livingstone:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.15/D19

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

Support: NIH R01-EY019924-08
Research to Prevent Blindness/ Lions Clubs International Foundation

Title: Neural correlates of dynamic human visual search in cerebral visual impairment using virtual reality simulation

Authors: *C. R. BENNETT[1,2], E. S. BAILIN[1,2], T. K. GOTTLIEB[1], C. M. BAUER[1,2], P. J. BEX[3], L. B. MERABET[1,2]
[1]Massachusetts Eye and Ear Infirmary, Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Northeastern Univ., Boston, MA

Abstract: *Background*:
Human visual search of a dynamic visual scene (e.g. finding a person in a crowd) involves many higher-level visual processing brain regions. Developmental complications can impair the function of these visual processing regions and thus impact visuospatial performance. Evidence suggests that individuals with cerebral visual impairment (CVI) often report difficulties identifying an individual in a crowd, particularly at higher crowd densities. However, the neural correlates of impaired dynamic human visual search in this population remain unclear. To investigate this, we developed a virtual reality (VR) environment and fMRI protocol to probe which brain regions may be responsible for impaired visual search performance in CVI.
Methods:

The virtual simulation invokes dynamic visual search by having participants find a target person among varying levels of distractors (i.e. 1 to 30 people) walking throughout a hallway scene. A cohort of individuals with CVI (ages 16-25, M = 19.5) and typically sighted controls (ages 14-28, M = 19.3) underwent behavioral testing and scanning. Behavioral testing was completed using desktop VR and the Tobii 4c eye-tracking system. Functional MRI data were acquired on a 3T Philips Achieva System for each participant.
Results:
Behavioral performance showed marked differences between the control and CVI groups for reaction time and quantified gaze data spread. Individuals with CVI: (1) took longer to identify the correct target, (2) had notably wider search patterns, and (3) exhibited even further impairment of visual search under conditions of higher task complexity, when compared to controls. Imaging data revealed that compared to controls, individuals with CVI demonstrated reduced functional activation in the fusiform face area (FFA), fusiform body area (FBA), intraparietal sulcus (IPS), and other higher visual processing areas. In particular, individuals with CVI show similar activation of the aforementioned visual areas regardless of task complexity, while controls showed increased activation with higher crowd densities. Additionally, a pattern of increased frontal activation was observed for the CVI group at both task complexities compared to controls.
Conclusions:
Current results suggest that individuals with CVI have difficulty performing a dynamic human visual search task. Increasing visual search demands (i.e. greater crowd size) had a more detrimental effect in the CVI group. Functional activation within higher order visual processing areas reflected the observed behavioral deficits. The aggregate of behavioral and imaging outcomes match reported real-world behaviors in the CVI population.

Disclosures: C.R. Bennett: None. **E.S. Bailin:** None. **T.K. Gottlieb:** None. **C.M. Bauer:** None. **P.J. Bex:** None. **L.B. Merabet:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.16/D20

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

Support: U01 AA014834
F32 AA022561

Title: Associations between white matter microstructure alterations and sensorimotor performance in adolescents with prenatal alcohol exposure

Authors: *K. A. UBAN[1], S. BODISON[3], E. KAN[1], E. R. SOWELL[2]
[2]Pediatrics, [1]Children's Hosp. Los Angeles, Los Angeles, CA; [3]Occup. Sci. and Occup. Therapy, USC, Los Angeles, CA

Abstract: Fetal alcohol spectrum disorder (FASD) is completely preventable, yet remains among the top 3 known causes of intellectual disability. Sensorimotor processing is impaired by prenatal alcohol exposure (PAE), and involves neurocircuitries that process sensory input, and then integrate with neurocircuitries to produce motor output. Very little is known about how PAE-related brain alterations relate to sensorimotor impairments with FASD. The present study aimed to fill this gap through examination of white matter microstructure and a sensorimotor battery. Diffusion tensor imaging (DTI) measures restriction of water diffusion known as fractional anisotropy (FA). We hypothesized that PAE would be associated with reduced FA in key sensorimotor circuitries, and would relate to poor sensorimotor performance. 30 directional DTI images were obtained in adolescents with PAE (boys: n=8, mean=11.7±2.5 years; girls: n=5, mean=13.6±2.6 years) and age- and sex-matched non-exposed peers as Controls (n=11) as part of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders at Children's Hospital Los Angeles. Along-tract statistics were utilized to investigate integrity of white matter at specific points along key tracts for sensorimotor processing [bilateral corticospinal tract (CST), Forceps major (Fmaj) and Forceps minor] across boys and girls, controlling for multiple Point by Tract comparisons at $p<0.05$. Sensory processing abilities and fine and gross motor skills were assessed with the Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) and the Sensory Profile 2 Questionaire. Associations between sensory and motor summary measures were examined with summary FA measures of key white matter tracts using Pearson correlations. Mean FA of the left CST ($p<.03$) and Fmaj ($p<.04$) were significantly associated with lower sensory and motor performance in adolescents with PAE, but not Controls. Follow-up analyses demonstrated that mean FA of was significantly associated with poorer balance and bilateral motor control in adolescents with PAE compared to Controls. Results provide preliminary evidence that poorer sensorimotor performance observed among individuals with FASD may relate to alterations in underlying white matter microstructure, specifically within tracts that integrate circuitry across the left and right hemispheres, and coordinate brain-spinal integration. Increased understanding of PAE-related alterations in sensorimotor neurocircuitries could inform future FASD-specific interventions targeted at improving sensorimotor integration in adolescents.

Disclosures: K.A. Uban: None. **S. Bodison:** None. **E. Kan:** None. **E.R. Sowell:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.17/D21

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

Support: Foundation for Ophthalmology Research and Education - International

Title: Development of sensory competition in the visual cortex: An fMRI study in school-aged children

Authors: *N. KIM, M. P. PINSK, S. KASTNER
Princeton Univ., Princeton, NJ

Abstract: The visual system is constantly bombarded with too much information to process at once. When multiple stimuli are present at the same time, they are not processed independently, but interact with one another to compete for sensory representation in the visual system (Desimone and Duncan, 1995). The neural mechanisms underlying sensory competition have been extensively studied in nonhuman primates and adult humans, but it remains unclear how such sensory interactions occur in the developing visual system. Here, we investigated competitive interactions among multiple objects in the visual cortex of adults and children (age 6 to 12) by using fMRI in the conceptual framework of biased competition theory. The amount of sensory competition was measured by comparing BOLD responses to multiple stimuli presented either simultaneously or sequentially in the periphery of the visual field. The spatial distance between the objects was also varied in order to modulate the amount of sensory competition as a function of receptive field (RF) architecture across the visual system. In adult participants, competitive interactions were scaled to RF sizes across the visual processing hierarchy, thereby corroborating previous findings. In contrast, in children, we found sensory competition effects in extrastriate areas beyond the RFs, thus including the extra-RF surrounds. These results suggest that, unlike adults, suppressive interactions from the extra-RF surrounds may contribute during development to mediate competition interactions among multiple objects that are simultaneously presented. Since selective attention operates on competitive interactions to filter out distracter information in the adult brain, this sort of filtering mechanism may be implemented quite differently in the developing brain. Future studies will be needed to address this issue.

Disclosures: N. Kim: None. **M.P. Pinsk:** None. **S. Kastner:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.18/D22

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

Support: MSCA ITN – ETN, grant 641652

Title: Signatures of auditory brain maturation and their relation to attention and response inhibition

Authors: *S. VAN BIJNEN[1], T. PARVIAINEN[2]
[1]Univ. of Jyväskylä, Jyväskylä, Finland; [2]Ctr. For Interdisciplinary Brain Res., Jyväskylä, Finland

Abstract: The sequence of brain responses to auditory stimulation are strikingly different in children compared to adults. In short, whereas the adult waveform is typically dominated by the short lived P1-N1-P2 responses, the child waveform is characterized by a peak around 100ms (referred to as P1 in EEG and P1m in MEG recordings) and one robust peak around 250ms after stimulus presentation (N250/N250m or N2/N2m). In primary school children (~6-11y), the emerging N1(m) overlaps in space and time with both the P1(m) and the N250(m). This complicates the separation and extraction of neurophysiological signatures that reflect distinct (auditory) processes, emphasizing the need to include source information in order to study the development trajectory and functional significance of these auditory responses. In this combined M/EEG and MRI study, we recorded auditory responses evoked by sine-wave tones in both active and passive tasks of 6-15 year old children. Source analysis was used to isolate the auditory responses. In the passive task, children were asked to ignore a standard (1 KHz) and deviant tone (1.5 KHz). The active tasks were divided in a detection task (press for deviant tone) and an auditory go/no-go (press for standard tone). Based on previous research we hypothesized an emergence of N100m with age accompanied by a decrease in P50m and N250m. We further anticipated increased N100m and decreased N250m responses in the active tasks compared to passive tasks. The results showed a decrease in P1m and N250m and an increase in N100m with age, as has been found in previous studies. This maturational trajectory is most clear in the right hemisphere; typically the dominant hemisphere for pure-tone processing in adults. Furthermore, in the inhibition task all except the youngest age group show a decrease in right-hemisphere N250m when it signals a need to inhibit your response, compared to the passive task. Conceivably, this neural inhibition can also be achieved by making the processing of the sound relevant for response inhibition. These results suggest that the functional significance of these signatures of auditory brain maturation extend beyond sensory sound analysis to include a broad range of cognitive processes important for everyday functioning.

Disclosures: S. Van Bijnen: A. Employment/Salary (full or part-time):; University of Jyväskylä. 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.; ChildBrain, Horizon2020 Marie Skłodowska-Curie Action (MSCA) Innovative Training Network (ITN) – European Training Network (ETN). Grant agreement no. 641652. **T. Parviainen:** A. Employment/Salary (full or part-time):; University of Jyväskylä.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.19/D23

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

Support: UGC JRF
CSIR 37(1420)/10/EMR-II

Title: Effect of in ovo sound stimulation on the development of auditory cortex and hippocampus of neonatal chicks

Authors: *P. KATHPALIA[1], T. C. NAG[1], M. BHAT[1], T. S. ROY[1], S. WADHWA[2]
[1]All India Inst. of Med. Sci., New Delhi Delhi, India; [2]Anat., North Delhi Municipal Corp. Med. Col., Delhi, India

Abstract: Sound exposure during development affects the Central Nervous System at multiple levels. There is an increase in neuronal number and size in brainstem auditory nuclei, auditory cortex and hippocampus in response to *in ovo* rhythmic sound stimulation at 110 dB in chicks. Chicks exposed to *in ovo* rhythmic/arrhythmic sound stimulation at the same sound intensity of 110 dB also show differences in their performance on a spatial memory task. Brain-derived Neurotrophic Factor (BDNF) levels have been found to be altered in central auditory system and hippocampus of the neonatal chicks, but in depth mechanisms are still not clearly known. To understand one such possible underlying mechanism in detail, we decided to study the epigenetic regulation of BDNF in these regions.
Eggs of fertilized white Leghorn chicks (*Gallus g. domesticus*) were exposed to rhythmic (sitar music frequency ranging from 100-4000Hz, serving as enriched environment) /arrhythmic (traffic noise, 30-3000Hz with peak frequency at 2700 Hz) sound stimulation at 110 dB from embryonic day 10 (E10) until hatching. At posthatch day 1, tissue samples were taken from brainstem auditory nuclei, auditory cortex and hippocampus for protein and RNA isolation and for Chromatin Immunoprecipitation (ChIP) to quantify levels of acetylated histone H2B and H4 at the Bdnf promoter region.
In auditory cortex, an increase in the levels of acetylated Histone H4 at the Bdnf promoter was observed in chicks exposed to *in ovo* rhythmic sound, but no changes w.r.t epigenetic marks on the Bdnf promoter were seen in the hippocampus. We further performed a Microarray analysis (Gene Expression Microarray by Agilent Technologies) of hippocampal RNA to look at differential gene expression, and found a total of 65 genes to be up regulated and 117 genes to be down regulated (analysis done by GeneSpring, Agilent Technologies), in the rhythmic sound stimulation group in comparison to the arrhythmic sound stimulation group in the neonatal hippocampus. The GO enrichment analysis revealed genes with GO terms for metabolic

processes, development, differentiation, cell communication, regulation of transcription, and morphogenesis.
Thus, *in ovo* sound stimulation affects epigenetic regulation of a growth factor in the auditory cortex that could explain the increased neuronal number and size. The effect on hippocampus would need to be further elucidated by a systemic evaluation of the results obtained from the microarray data. Further, it is essential to understand the auditory cortex and hippocampus circuitry and connectivity during the development of CNS to gain insights into the effect of *in ovo* sound stimulation on spatial memory.

Disclosures: P. Kathpalia: None. **T.C. Nag:** None. **M. Bhat:** None. **T.S. Roy:** None. **S. Wadhwa:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.20/D24

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

Support: DFG Grant CRC 870
DFG Grant RTG 2175
German Federal Ministry of Education and Research [01 GQ 1407]

Title: Xenoplastic transplantation of inner ears reveals conserved afferent targeting and circuit formation in hindbrain vestibular networks

Authors: *C. GORDY[1], B. FRITZSCH[2], H. STRAKA[3]
[1]Dept. Biol. II, Ludwig-Maximilians-University Munich, Planegg, Germany; [2]Dept. of Biol., Univ. of Iowa, Iowa City, IA; [3]LMU Munich - Biocenter Martinsried, Planegg, Germany

Abstract: A major step in the developmental formation of vestibular circuitries is the establishment of specific afferent connections between inner ear organs and functionally matching sets of central vestibular neurons. The diversity and segmental arrangement of the different vestibular phenotypes during ontogeny depends on the combinatorial expression of developmentally regulated genes along the rhombomeric scaffold. This genetic and cellular patterning also promotes and influences the target finding of developing vestibular afferents. Given the genetic conservation of inner ear and hindbrain patterning during vertebrate ontogeny, such connectivity specification might be conserved across distant species. Thus, inner ear afferents from different species should be able to connect, if presented with foreign hindbrain environments. Here, we experimentally tested an adequate establishment of connections between inner ears and the vestibular nuclei following unilateral xenoplastic inner ear transplantations between two distant amphibian species, *Xenopus laevis* and *Ambystoma mexicanum* (Axolotl).

Single inner ear vesicles from both species were removed and reciprocally transplanted to replace the removed ear at comparable embryonic stages. This ear vesicle swap method therefore generates *Xenopus* embryos (stage 33) with a grafted inner ear from an Axolotl (stage 38) donor, and *vice versa*. Following transplantation, manipulated embryos of both species were reared until reaching early larval stages to assess the development of VIIIth nerve afferents and their innervation of the vestibular nuclei. Injections of lipophilic neuronal tracer (NeuroVue) into native and transplanted ears were used to label afferent vestibular projections. Following dye diffusion for 17 hours, bundles of afferent fibers from transplanted and control ears were labeled in both Axolotl and *Xenopus*, respectively. Afferent fiber bundles from grafted and native ears entered the hindbrain in rhombomere 4, bifurcated rostrally and caudally, and innervated the entire longitudinal extent of the vestibular nuclei. This now allows testing the establishment of functional connections between xenoplastic afferents and central vestibular neurons by recording vestibulo-ocular reflexes during natural stimulation at later developmental stages. These results suggest the presence of ubiquitous and species-independent genetic/molecular guidance cues that provide an ontogenetic environment for vestibular afferents that is shared in all vertebrates and allows formation of adequate connections between inner ear organs and central neuronal circuits.

Disclosures: C. Gordy: None. **B. Fritzsch:** None. **H. Straka:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.21/D25

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

Support: MN State Uni. Mankato Dept. of Biological Sciences
Intramural program at NIDDK at NIH

Title: Quantification and localization of carbohydrate sulfotransferase (Chst15) in developing hypothyroid cochlea

Authors: *M. C. TOMPACH[1], D. FORREST[2], D. S. SHARLIN[1]
[1]Biol. Sci., Minnesota State University, Mankato, Mankato, MN; [2]NIDDK, NIH, Bethesda, MD

Abstract: Thyroid hormone (TH) is necessary for proper auditory system development and hearing. The greater epithelial ridge (GER), a transient cochlear structure important in tectorial membrane formation, is remodeled in the early postnatal cochlea and timing of GER remodeling is influenced by TH. In developing hypothyroid cochlea, regression of the GER is delayed which leads to sustained secretion of tectorial membrane proteins and altered tectorial membrane structure. Although it is clear that TH controls GER remodeling, the TH responsive genes that contribute to this phenotype are largely unknown. Through a transcriptional screen performed on

isolated GER cells, carbohydrate sulfotransferase 15 (Chst15) was identified as a potential TH responsive gene in the GER. Chst15 is a type II transmembrane glycoprotein that acts as a sulfotransferase to transfer sulfate to the C-6 hydroxal group of chondroitin sulfate. Interestingly, several studies have localized chondroitin 6-sulfate proteoglycan epitopes to the tectorial membrane. Moreover, Chst15 has been implicated in the deafness associated with headbobber (*hb*) mutant mouse line. Chst15 is one of three genes deleted as a consequence of the insertional mutation. The *hb/hb* mice have a number of inner ear abnormalities including an abnormal tectorial membrane and disorganized hair cell stereocilia. Considering this, we hypothesize that Chst15 is a TH responsive gene and its expression is misregulated in the developing hypothyroid cochlea contributing to the deafness associated with low TH. To test this, hypothyroidism was induced in timed-pregnant dams starting at embryonic day 12.5 (E12.5). Untreated euthyroid dams served as controls. Cochlea from pups were harvested at E16.5, postnatal day (P)1, P5, P10, and P15. Chst15 mRNA was quantified by qRT-PCR and its tissues distribution was mapped using *in situ* hybridization. Our results indicate that Chst15 is developmentally regulated with expression decreasing as development proceeds. Additionally, hypothyroidism delayed the decrease in Chst15 mRNA observed in euthyroid controls. This observation is consistent with the known effect of hypothyroidism on GER remodeling. *In situ* hybridization demonstrated that the expression of Chst15 mRNA is largely restricted to the GER with low levels observed in the other cochlear regions. Based on the reported function of Chst15, these results suggest that Chst15 may play an important role in sulfonating tectorial membrane proteins. Additionally, these results provide some insight in to the cochlear abnormalities associated with low TH.

Disclosures: M.C. Tompach: None. **D. Forrest:** None. **D.S. Sharlin:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.22/D26

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

Support: NSERC #312015

Title: Early developmental expression of $P2X_2$ and $P2X_3$ purinergic receptors in cephalic tissues of opossums Monodelphis domestica

Authors: *A. BEAUVAIS, J.-F. PFLIEGER
Sci. Biologiques, Univ. de Montreal, Montreal, QC, Canada

Abstract: The P2X cation-channels are a family of ATP-gated purinergic receptors, comprising seven identified subtypes, that are distributed throughout the nervous system. Little is known of their physiological roles in nervous system ontogenesis, such as in mammalian sensorimotor

development. Given its immature state at birth which compares to that of a 13 day rat embryo, we use the opossum *Monodelphis domestica*, a marsupial, as a model to investigate the ontogenesis of sensorimotor systems. A previous study using *in vitro* preparations of newborn opossums has shown that PPADS, a non-specific P2 purinoceptors antagonist, decreases the intensity of forelimb motor responses induced by mechanical stimulations of the face. This suggests that some purinergic receptors may be involved in early sensorimotor transmission. We have used immunofluorescence to investigate the developmental expression of $P2X_2$ and $P2X_3$ in cephalic tissues of opossums aged from one day after birth (P1) to P14. These two receptors were targeted since they are expressed in the brain of embryonic rats and are the most common subtypes on sensory neurons in mature rodents. We found that $P2X_2$ labeling appeared only at P5 in opossums. At this age, it was observed in a small number of cells in the trigeminal ganglia and in several nerve fibers at the periphery of the brainstem. $P2X_2$ labeling remained sparse after P5. In contrast, $P2X_3$ labeling was present in the facial skin (including the ears pinnae) of P1 opossums, where it was observed in the dermis and around growing hairs. Its intensity increased afterwards. Moreover, diffuse $P2X_3$ labeling was present throughout the trigeminal ganglia at all ages studied. In the central nervous system, the whole brainstem showed a strong background labeling at P1 and P5, preventing identification of individual cells. At P9 the labeling was less intense and cells could be identified in some brainstem nuclei and in the cerebral cortex. Our findings suggest that $P2X_3$ purinergic receptors could potentially be involved in physiological mechanisms underlying early sensorimotor functions in opossums, but this is doubtful for $P2X_2$. Pharmacological experiments will be undertaken to better characterize the role of the $P2X_3$ receptors.

Disclosures: A. Beauvais: None. **J. Pflieger:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.23/D27

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

Support: NSERC #312015

Title: Distribution of the mechanically activated channel Piezo2 in the facial skin of developing opossums, Monodelphis domestica

Authors: *J. LAFORGE, J.-F. PFLIEGER
Sci. Biologiques, Univ. de Montreal, Montreal, QC, Canada

Abstract: Marsupials such as opossums of the species *Monodelphis domestica* are born very immature. The newborns use their forelimbs to crawl on the mother's belly and attach to her

nipples to pursue their development. Sensory cues are needed to sustain the locomotor behavior, guide the newborn to the nipple and trigger the attachment. We have demonstrated the presence of numerous nerve fibers from the trigeminal nerve in the facial skin in the newborn and that mechanical pressures exerted on the facial skin provokes forelimb movements, indicating that trigeminal nerve fibers have mechanosensory properties. The stimuli employed may be have been sensed by mechanosensory or nociceptive free endings, and/or by Merkel cells, the latter being epidermal mechanoreceptors. To pursue further this line of study, herein we look at the distribution of Piezo2 in the facial skin of newborn opossums. Piezo2 is a stretch-gated cationic channel that has been shown to be involved in mechanotransduction by Merkel cells and their innervating fibers, at least in mature mammals. 9 opossums aged from one day after birth (P1) to P14 were used for the present study. Each animal was anesthetized by hypothermia until it was unresponsive to stimulation. It was then decapitated and its head fixed by immersion in 4% paraformaldehyde. The head was sectioned transversally with a cryostat and the sections were processed for immunofluorescence using a rabbit polyclonal anti-Piezo2 (Sigma-Aldrich) as a primary antibody. They were then incubated with a secondary antibody, which was conjugated to a fluorophore, and were observed using a microscope equipped for fluorescence. No labeling was found in the facial skin at P1 and P7. At P13-14, labelled cells were observed in the root sheath of numerous hair follicles on the cheeks and the snout, but not in control sections of the same specimens processed without the primary antibody. Labeling was not seen in the cephalic ganglia or the brainstem. From these results we conclude that Piezo2 cannot be involved in the mechanosensory responses of the newborn opossum. The labelled cells expressing Piezo2 in older postnatal opossums may be Merkel cells, which are present on hair follicles in mammals, but this needs to be verified.

Disclosures: J. Laforge: None. **J. Pflieger:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.24/D28

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

Support: Swedish Research Council

Title: Neuropeptides in the developing mouse brain

Authors: J. BAKKER[1], S. S. BARDE[1], S. STEFFENS[1], F. GIRACH[2], B. SZAROWSKA[2], I. ADAMEYKO[2], K. MELETIS[1], *T. G. HOKFELT[3], T. HARKANY[1]
[1]Karolinska Institutet, Stockholm, Sweden; [2]Med. Univ. of Vienna, Ctr. for Brain Res., Vienna, Austria; [3]Neurosci., Karolinska Inst. - Biomedicum, Stockholm, Sweden

Abstract: Dynamic changes in the expression of several neuropeptides during (mouse) brain development have previously been reported, including CCK, NPY and vasopressin. Moreover, several neuropeptides were found to affect typical events in neuronal development, such as mitosis, neuronal survival, sprouting and differentiation, classifying them as neurotrophic factors. However, some caution is warranted when interpreting these data: as the neuropeptides were almost exclusively administered exogenously either *in vivo* or *in vitro*, the observed receptor response may not have been physiological. Still, these early results pointed at a potential role of several neuropeptides as neurotrophic factors. Interestingly, many neuropeptide null mouse lines have demonstrated behavioral changes and even loss of specific neuronal populations, although the absence of a neuropeptide does not necessarily lead to a serious or lethal phenotype, possibly because of redundancy in neuropeptide signalling. In the Galanin-Cre::Tomato mouse we found, surprisingly, Galanin-Tomato^{+} cell bodies in the ventrobasal complex of the thalamus (VB) from P4 onwards, which was confirmed by CUBIC clearing in the adult mouse brain. To confirm endogenous galanin expression we carried out histochemical analyses in the VB. Using radioactive riboprobe and *in situ* hybridization we found low preprogalanin mRNA levels at E18, increased levels at P7, and no expression in the adult, indicating transient expression of preprogalanin mRNA. With immunohistochemistry we detected galanin peptide (and galanin message-associated peptide, GMAP) in cell bodies in VB from P4-14. From P21, only a few galaninergic fibers were found randomly dispersed throughout the VB. In the Galanin-Cre::Tomato mouse, Tomato^{+} fibers were present in barrel cortex, seemingly following the pattern of barrel formation. Weak galanin (and GMAP) labelling was detectable in barrels from P4-14. From P21, galanin was present in scattered fibers throughout the cortex. AAV-GFP injections into VB of Gal-Cre::Tomato mice at P7 showed that galaninergic cells in the VB project towards the barrel cortex. Taken together, our findings indicate a role for galanin in the development of the somatosensory system.

Disclosures: J. Bakker: None. **S.S. Barde:** None. **S. Steffens:** None. **F. Girach:** None. **B. Szarowska:** None. **I. Adameyko:** None. **K. Meletis:** None. **T.G. Hokfelt:** None. **T. Harkany:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.25/D29

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

Title: Type III Neuregulin 1 potentiates TrkA signaling in sensory neurons through activation of src family kinases

Authors: *S. LONCAR[1], L. W. ROLE[2], D. A. TALMAGE[3]
[2]Neurobio. & Behavior, [3]Pharmacol. Sci., [1]Stony Brook Univ., Stony Brook, NY

Abstract: During development, nociceptive sensory neurons depend on the neurotrophin nerve growth factor (NGF) for survival. NGF is produced by peripheral target fields of sensory axons and by activating the receptor tyrosine kinase, TrkA, sends a survival signal to the neuronal soma in the dorsal root ganglia (DRG). In the absence of either NGF or TrkA, these neurons undergo axon degeneration and then apoptosis. Genetically blocking apoptosis prevents neuronal cell death, but not axon degeneration. Type III Neuregulin 1 (Nrg1) is also required for the survival of $TrkA^{+}$ sensory neurons. When apoptosis is blocked in Type III $Nrg1^{-/-}$ mice, sensory neuron central projections to the spinal cord are maintained while peripheral projections reach their target fields but eventually retract and degenerate: a phenotype highly reminiscent of NGF and TrkA mutants, as well as mutants lacking the ERK1 and ERK2 in sensory neurons. Based on the similarities between NGF, TrkA, and Type III Nrg1 mutants, I hypothesized that Type III Nrg1 was necessary to achieve optimal levels of NGF-TrkA signaling. In this study, I demonstrate that Type III Nrg1 participates in NGF-TrkA signaling via regulation of Src family kinases (SFKs). I find that DRG neurons from Type III $Nrg1^{-/-}$ embryonic mice have lower levels of active SFK and of ERK1/2 in the absence of and in response to NGF compared to wild type littermates. I show that in embryonic DRG neurons, SFK activity is required for maximal NGF-TrkA activation of the MAP kinase pathway. The convergence of SFK and TrkA signaling on the MAP kinase pathway enhances axon outgrowth. I further demonstrate that Type III Nrg1 forms a complex with Src via a proline-rich SH3 ligand and that Type III Nrg1 can be tyrosine phosphorylated by Src. I show that re-expression of Type III Nrg1 in mutant sensory neurons rescues deficits in axon outgrowth as well as SFK and ERK1/2 activation but expression of a mutant Type III Nrg1 that fails to interact with Src does not rescue these deficits. These results demonstrate for the first time that Type III Nrg1 regulates SFK activity and that regulation by Type III Nrg1 is critical for NGF-TrkA signaling in nociceptive sensory axons during development. Results are from 3 independent experiments and axon measurements were made while blind to genotype.

Disclosures: S. Loncar: None. **L.W. Role:** None. **D.A. Talmage:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.26/D30

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

Support: FRIA Grant

Title: Onecut transcription factors control the development of sensory neurons in the dorsal root ganglia

Authors: *G. MASGUTOVA, A. HARRIS, F. CLOTMAN
Lab. of Neural Differentiation, Univ. Catholique De Louvain, Brussels, Belgium

Abstract: Without sensory neurons, one could perceive neither touch, cold, limb movements or spatial position nor pain. Three major classes of sensory neurons, in cranial or dorsal root ganglia (DRG), enable to sense and distinguish these stimuli. Their differentiation is characterized by the early expression of tyrosine kinase receptors for neurotrophic factors (Trk). Small diameter TrkA+ neurons are activated by noxious stimuli, medium diameter TrkB+/C+ neurons are mechanoreceptors and large diameter TrkC+ neurons convey proprioceptive information. Transcription factors of the Onecut family, namely OC-1 and OC-2, are present in sensory neurons during embryonic development. To assess the roles of these factors during DRG development, we phenotypically analysed mouse embryos mutant for the Onecut genes from embryonic day e10.5 to e16.5.
We observed that DRG sensory neurons devoid of Onecut factors showed a decrease in the number of TrkA+ sensory cells at developmental day e10.5. However, the number of TrkA+ cells rapidly normalized, suggesting a delay in TrkA expression onset. In addition, we observed an increase in TrkB+/TrkC+ coexpression resulting from a higher proportion of TrkB+ cells. From e14.5, this imbalanced expression of TrkB/C normalized and reached a distribution similar to that of control littermates. To identify the cause of these defects, we assessed cell proliferation and death in the developing DRG. Our preliminary data suggest alterations of proliferation and of apoptosis of sensory neurons in Onecut mutant embryos. Hence, our observations demonstrate that Onecut proteins are involved in the differentiation of sensory neurons and may control the onset of Trk expression.

Disclosures: G. Masgutova: None. **A. Harris:** None. **F. Clotman:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.27/D31

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

Support: NIH Grant EY027347
NIH Grant NS085176
Craig H. Neilsen Foundation
BrightFocus Foundation

Title: Mapping function-related epigenomes in mouse dorsal root ganglia neurons

Authors: *C. QIAN[1], Q. LI[2], X. WANG[3], C. ZHANG[3], T. LIN[3], A. KOSANA[3], B. C. DONG[1], F.-Q. ZHOU[4]
[1]Orthopedic Surgery, JHMI, Baltimore, MD; [2]Orthopedic Surgery Dept., Johns Hopkins Hosp., Baltimore, MD; [3]Neurosci., Johns Hopkins Univ., Baltimore, MD; [4]Orthopedic surgery and Neurosci, Johns Hopkins Univ. Sch. Med., Baltimore, MD

Abstract: The mammalian sensory neurons with somas in the dorsal root ganglia (DRG) branch axons into CNS and PNS. DRG neuron serves as a prevailing model for studies of neurodevelopment, neuropathy and particularly axon regeneration. The peripheral branch of DRG neurons can regenerate axons after injury, but the CNS end cannot. Intrinsic regenerative capacity related to gene transcription has garnered growing interest after a study showing that preconditioning PNS-end lesion can promote axon regeneration at the CNS end. In fact, early studies using microarrays and recent whole-genome sequencing at the single-cell level revealed that various genes especially some regeneration-associated genes (RAGs) changed in DRG neurons after sciatic nerve axotomy. These RAGs are associated with cellular functions including metabolism, protein synthesis, axonal trafficking and cell death. Such widespread transcriptional alterations suggest that the axon regeneration in the PNS is coordinated by various categories of genes. In addition, even though developed DRG neurons in adult mammalians can reactivate axon regeneration after injury, DRG neurons still show a developmental decline in the regenerative capacity, which suggests a step-wise closure of regenerative transcriptional programs along the developmental stages. All of these suggest that the intrinsic capacity of DRG neuron axon regeneration is a reflection of specific favorable chromatin architecture that allows a whole set of RAGs to be accessed and transcribed. Indeed, emerging evidence has demonstrated the role of histone posttranslational modification and DNA methylation in DRG neuron axon regeneration. For next step of the study, several unbiased deep-sequencing-based epigenome mapping techniques are suitable for further dissecting the mechanisms in detail. However, the heterogeneity of cells in the DRG challenges such study. The non-neuronal DRG cells (>50%), particularly the satellite glia tightly adhering to somas of DRG neurons and migrated macrophages have been shown to undergo epigenetic alterations as indirect responses to nerve injury. With the elimination of these interferences, we are analyzing how TFs, histone markers and regulators influence the widespread transcriptional programs in DRG neurons during processes including but not limited to neurodevelopment, nerve injury and axon regeneration. These data will help to obtain insights into some unique and useful properties of DRG neurons regarding the epigenetic regulation. With the full potential of such method, we should be able to obtain some knowledge regarding the intrinsic properties of various subtypes of DRG neurons.

Disclosures: C. Qian: None. **Q. Li:** None. **X. Wang:** None. **C. Zhang:** None. **T. Lin:** None. **A. Kosana:** None. **B.C. Dong:** None. **F. Zhou:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.28/D32

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

Support: National Natural Science Foundation of China No. 31660289
National Natural Science Foundation of China No. 81260175
National Natural Science Foundation of China No. 81560198

Title: Morphological and electrophysiological development of rat spinal substantia gelatinosa neurons

Authors: *J. WU[1], S.-C. PENG[1], H.-X. KUANG[1], D.-Y. ZHANG[2], L.-M. CHEN[1], L.-L. XU[1], T. LIU[2]
[1]Nanchang Univ., Jiangxi, China; [2]The First Affiliated Hosp. of Nanchang Univ., Nanchang, China

Abstract: Aim:Spinal lamina II, also known as substantia gelatinosa (SG), consists of a heterogenous population of neurons that process incoming sensory signals before information ascending to the brain. Previous study shows developmental changes in electrophysiological properties of superficial dorsal horn neurons from P0-5 and P24-45 mice (Tadros et al., 2012), but the neuroanatomical basis for these changes is not known. Moreover, the prevalence of many types of chronic pain peaks in midlife (Gagliese et al., 2000), suggesting the necessity to expand the ages to middle-aged animals in developmental research. Methods:Four age groups of male and female Sprague-Dawley (SD) rats were recruited: neonate (aged 7 days), juvenile (aged 3 weeks), young adult (aged 6-8 weeks) and middle-aged (8-12 months). Whole-cell patch-clamp recordings were performed to record the electrophysiological properties of SG neurons from acute parasagittal lumbar spinal cord slices. Morphological properties of neurobiotin-filled SG neurons were observed under a confocal microscopy. Results:Altogether, 381 SG neurons from neonate (n = 129 cells), juvenile (n = 124 cells), young adult (n = 94 cells) and middle-aged (n=34 cells) rats were used for morphological analysis. Four major cell types based on their morphology were identified: islet, central, radial, and vertical cells. The proportions of islet and central neurons were significantly increased in young adult group compared to neonatal rats. However, we observed a decrease of them in middle-aged group compared to young adult group. In contrast, the percentages of vertical and radial neurons were dramatically decreased in middle-aged group compared to neonatal group. Furthermore, the densities of spine and bouton exhibit highest level in juvenile and adult groups, respectively. Based on the electrophysiological data, seven firing patterns of SG neurons were observed: tonic-firing, delayed-firing, single-spike, initial-burst, phasic-bursting, gap-firing, and reluctant-firing. The percentage of tonic-firing was

highest in neonates compared to other age groups. In addition, the proportion of sub-threshold currents, such as hyperpolarization-activated inward currents (I_h) and A-type potassium currents (I_A), were highest in juvenile and adult groups, respectively. Conclusions:Our results demonstrate age-dependent morphological and electrophysiological changes in SG neurons. These structural and functional differences may have important implications that contribute to age-related pain behaviors.

Disclosures: J. Wu: None. **S. Peng:** None. **H. kuang:** None. **D. Zhang:** None. **L. Chen:** None. **L. Xu:** None. **T. Liu:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.29/D33

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

Title: Hypothalamic inflammatory and barrier changes in rodent offspring born of females following surgical weight loss

Authors: *R. A. SPANN, C. A. ZAMARRIPA, N. ARAVINDAN, B. DUNCAN, B. E. GRAYSON
Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: Surgical weight loss has a positive impact on reproductive capabilities of women in addition to effectively treating obesity and diabetes. Despite improvement in maternal health, offspring of mothers who have had bariatric surgery may be born small-for-gestational age and are consequently at a much greater risk of metabolic disease as adults. The etiology of this relationship remains unknown. We have previously shown in a maternal rat model of vertical sleeve gastrectomy (VSG) greater permeability of the placental barrier, elevated inflammatory signaling, and higher incidence of apoptosis in the placenta. In the present study, we investigate outcomes in postnatal day (PD) 22 and 110 pups, measuring molecular and cellular changes in the hypothalamus. Here there is an increase in hypothalamic interleukin 1 beta mRNA (IL1B) expression in PD22 pups born to VSG dams when compared to pups from sham operated dams. Immunohistochemical detection of IBA1 positive microglia in the paraventricular nucleus of the hypothalamus shows reduced staining density in VSG pups with no impact on astrocyte density. We also report reductions in endothelial marker, RECA, in the arcuate nucleus of the hypothalamus in VSG pups in comparison to controls suggestive of altered capillary density. Finally, these are accompanied by reductions in TJP (tight junction protein) mRNA and increased claudin 5 mRNA expression in PD22 hypothalamus of VSG offspring. In PD110 female VSG offspring, we report increased expression of hypothalamic IL1B and IL6 mRNA in comparison to Sham offspring; these mRNA changes were not evident in male VSG offspring.

These results show that maternal VSG has effects early postnatal and long-term inflammatory and barrier function of the hypothalamus. Future work will determine if these changes are responsible for impaired metabolic control and weight gain.

Disclosures: R.A. Spann: None. **C.A. Zamarripa:** None. **N. Aravindan:** None. **B. Duncan:** None. **B.E. Grayson:** None.

Poster

642. Structural and Functional Development of Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 642.30/D34

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

Title: A comparative analysis of the visual system in two whale species

Authors: *M. A. SMITH[1], E. S. PLYLER[1], J. C. GEORGE[4], J. THEWISSEN[2], S. D. CRISH[3]
[2]Anat. and Neurobio., [3]Pharmaceut. Sci., [1]Northeast Ohio Med. Univ., Rootstown, OH; [4]Dept. of Wildlife Mgmt., North Slope Borough, Barrow, AK

Abstract: The whale visual system is a product of unique selection pressures, yet relatively little is known about it across taxa. We examined the general organization of retinas and optic nerves from beluga and bowhead whales in comparison to related terrestrial animals. The beluga retina presents with thinner synaptic and nuclear layers compared to the bowhead and other artiodactyls. While this “compression” could be attributed to a reduced density of cells and synaptic connectivity in most layers, the thin photoreceptor layer in the beluga is directly attributed to short outer segments. In the bowhead whale, previous reports indicate the absence of cone outer segments retina, we have histological data suggesting that a population of cone photoreceptors retain their outer segment. Comparing the ganglion cell layers, both the beluga and bowhead reveal smaller cell density in this layer with large, often displaced retinal ganglion cells predominating. Optic nerve analysis further reveals a greater density of larger caliber axons in these animals. These unique anatomical features will be discussed as it relates to particular challenges in whale vision.

Disclosures: M.A. Smith: None. **E.S. Plyler:** None. **J.C. George:** None. **J. Thewissen:** None. **S.D. Crish:** None.

Poster

643. Development of Motor, Sensory, and Limbic Systems: Limbic System

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 643.01/D35

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

Support: NIH Grant Z01 ES100221

Title: Novel role for mineralocorticoid receptors in the development and maintenance of hippocampal area CA2 pyramidal cell phenotype

Authors: K. E. MCCANN, D. J. LUSTBERG, K. E. CARSTENS, *S. FARRIS, E. K. SHAUGHNESSY, M. ZHAO, G. M. ALEXANDER, S. M. DUDEK
NIEHS/NIH, Research Triangle Park, NC

Abstract: In the brain, glucocorticoid (GR) and mineralocorticoid (MR) receptors mediate behavioral and physiological responses to stress. In the adult mouse hippocampus, the distribution of GRs and MRs is subregion-specific, with the highest MR:GR mRNA ratio being in area CA2 ($F(3,8)=40.51$, $p<0.0001$). In addition to the striking MR:GR ratio, CA2 pyramidal neurons exhibit a unique pattern of gene expression that tightly regulates synaptic plasticity, further distinguishing it from its hippocampal neighbors. MRs are expressed in the embryonic hippocampus and may be one of the earliest markers for CA2. Although much is known about MR function in stress response, the biological significance of this early and concentrated MR expression in CA2 remains unknown. Thus, the goal of the current study was to investigate the role of MRs in the development and maintenance of CA2 molecular and cellular identity, including its distinct plasticity phenotype. Using immunofluorescence, we assessed whether CA2 pyramidal cell phenotype was changed by neuronal MR deletion. Indeed, we found that the expression of several of the molecules that make CA2 molecularly distinct, including RGS14, PCP4, and NECAB2, were reduced, regardless of whether MR deletion occurred embryonically (Nestin-Cre; whole brain neuronal MR knockout), postnatally, after postnatal day 4 (Amigo2-Cre; CA2-specific MR knockout), or in adulthood (virally expressed Cre in CA2). Interestingly, several CA1 markers, such as GR and WFS1, increased in the CA2 region after MR deletion, indicating that not only did the CA2 molecular phenotype disappear, but that CA2 took on a CA1-like phenotype. These results indicate that the genes that make CA2 molecularly distinct are under direct or indirect transcriptional control of MR. In addition, mRNA analysis of whole hippocampal extractions confirmed the results from our protein analysis and further revealed several stress-related genes that were also differentially expressed between Cre-negative and Cre-positive animals, including *Fkbp5*, which is normally highly expressed in CA2. Lastly, this loss of MR, and/or the resulting disruption of CA2 gene expression, enabled synaptic potentiation of the normally LTP-resistant synaptic currents in CA2 stratum radiatum. Together,

these results indicate MRs are critical for the development and maintenance of CA2 cellular phenotype. This novel role of MRs provides additional insight into their potential role in regulating CA2-mediated stress responses, including social behavior and aggression.

Disclosures: K.E. McCann: None. **D.J. Lustberg:** None. **K.E. Carstens:** None. **S. Farris:** None. **E.K. Shaughnessy:** None. **M. Zhao:** None. **G.M. Alexander:** None. **S.M. Dudek:** None.

Poster

643. Development of Motor, Sensory, and Limbic Systems: Limbic System

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 643.02/D36

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

Support: NIH grant MH100029-06
NIH grant MH078105-01S1
NIH grant MH078105-04S1
NIH grant MH096773
NIH grant MH086633
NIH grant U54 HD079124
NIH grant K99/R00 MH091238

Title: Development of amygdala-prefrontal cortex circuits in primates: A longitudinal neuroimaging study in infant macaques

Authors: *Z. A. KOVACS-BALINT[1], J. STEELE[2], E. J. FECZKO[6,7], O. MIRANDA-DOMINGUEZ[6], M. PINCUS[2], E. L. MORIN[2], E. EARL[6], L. LI[8,3], M. STYNER[9], J. BACHEVALIER[1,4], D. FAIR[6], M. SANCHEZ[1,5]
[1]Yerkes Natl. Primate Res. Ctr., [3]Dept. Pediatrics, [4]Dept. Psychology, [5]Dept. Psychiatry & Behav. Sci., [2]Emory Univ., Atlanta, GA; [6]Behavioral Neurosci., [7]Dept. of Med. Informatics and Clin. Epidemiology, Oregon Hlth. Sci. Univ., Portland, OR; [8]Marcus Autism Ctr., Atlanta, GA; [9]Dept. Psychiatry, Univ. of North Carolina, Chapel Hill, NC

Abstract: Primate infants develop critical social and emotional regulatory skills as they transition from dependence on their mothers to increased exploration and social interactions with peers during weaning. However, we still do not understand the underlying neurobiological processes. The goal of this study was to characterize the developmental changes of brain networks underlying socioemotional regulation, focusing on the structural and functional maturation of the amygdala (AMY) and its functional connectivity (FC) with prefrontal cortex (PFC) in infant rhesus monkeys. Structural and resting-state functional MRI (rsfMRI) scans were acquired longitudinally (at 2, 4, 8, 12, 16, 20 and 24 weeks - equivalent to 2 years in humans) in 16 male infant macaques living with their mothers in complex social groups. Structural T1- and

T2-MRI, and BOLD contrast sensitive rsfMRI scans were acquired using a 3T MRI scanner under isoflurane anesthesia. Developmental volume growth of AMY and PFC (gray + white matter) in relation to total brain growth (measured as intracranial volume -ICV-), and changes in AMY-PFC FC were analyzed throughout infancy using repeated measures ANOVA and network analysis. The potential confounding effect of anesthetics on FC was controlled for by adding anesthetic levels as covariates in the statistical models. Our results indicate that AMY volume sharply increases between 4-8 and again between 16-20 weeks, whereas the PFC volume sharply increases up to 4 months of age. After correcting the data with ICV, the proportion of the AMY increased, but the PFC decreased by age. The fast structural growth of AMY could support the sharp increase in positive FC between AMY and dorsolateral PFC regions (dlPFC: BA9, BA46), which contrasts with increased negative coupling between AMY and orbitofrontal cortex (OFC: BA11, BA13) observed after 8 weeks of age. Interestingly, AMY and medial PFC (mPFC: BA14, BA24, BA25, BA32) FC remained unchanged during the first 6 months of life, with some areas, such as the anterior cingulate (BA24), already showing positive FC with AMY soon after birth. Network analysis confirmed the PFC region-specific FC developmental patterns. Thus, AMY and PFC undergo drastic changes during the first 6 months of life and AMY-PFC circuits critical for social and emotional regulation become more strongly connected during infancy, with PFC region-specific developmental trajectories. These dynamic maturational changes in structure and AMY-PFC FC during the first 6 months of life probably tune the development of cortical brain regions and drive the transition to independence from the mother towards social interactions with other members of the group.

Disclosures: J. Steele: None. **E.J. Feczko:** None. **O. Miranda-Dominguez:** None. **M. Pincus:** None. **E.L. Morin:** None. **E. Earl:** None. **L. Li:** None. **M. Styner:** None. **J. Bachevalier:** None. **D. Fair:** None. **M. Sanchez:** None.

Poster

643. Development of Motor, Sensory, and Limbic Systems: Limbic System

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 643.03/D37

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

Support: Academy of Finland
Jane and Aatos Erkko Foundation
Sigrid Juselius Foundation
Doctoral Program in Brain and Mind

Title: The role of kainate receptors in the development of amygdala internal glutamatergic circuit in neonatal rats

Authors: *M. RYAZANTSEVA[1], J. E. ENGLUND[2], A. SHINTYAPINA[2], S. E. LAURI[2]
[1]Helsinki Univ., Helsinki, Finland; [2]Univ. of Helsinki, Helsinki, Finland

Abstract: Kainate-type glutamate receptors (KAR) have been linked to several developmentally originating CNS disorders related to dysfunction of the limbic areas, including mood and anxiety disorders, autism and schizophrenia. Despite the prospective clinical importance, nothing is known on the physiological functions of KAR in the developing amygdala. Here, RT-qPCR and in situ hybridization measurements were performed to characterize the expression pattern of KAR subunits in the amygdala during early postnatal development. The data obtained demonstrate KAR subunits and in particular, GluK1, GluK2 and GluK5 are highly expressed in the BLA and CeA during the first week of life in rodents. Whole-cell patch-clamp recordings of miniature EPSCs at different stages of postnatal development demonstrate that this time period coincides with an abrupt increase in functional glutamatergic inputs to basal and central amygdala. The contribution of KAR to transmission at the immature glutamatergic synapses was studied using selective pharmacological tools to manipulate KAR function during electrophysiological recordings. The synapses development was analyzed with confocal imaging of spines in amygdaloid nuclei at different ages. In addition, shRNA knock-down of KARs in the lateral amygdala was performed in vivo to investigate the role of KAR in the development of glutamatergic circuits between amygdaloid nuclei. The data obtained support that tonically active presynaptic KARs regulate glutamate release and development of the intra-amygdaloid connectivity during early postnatal development. Additional experiments with whole-cell recordings and pharmacological manipulations with signalling molecules demonstrated that KARs regulate presynaptic function by affecting activity of voltage-gated calcium channels.

Disclosures: M. Ryazantseva: None. **J.E. Englund:** None. **A. Shintyapina:** None. **S.E. Lauri:** None.

Poster

643. Development of Motor, Sensory, and Limbic Systems: Limbic System

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 643.04/D38

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

Support: P01NS083513
MH103003

Title: Childhood maturation of immature neurons in the human paralaminar amygdala

Authors: *S. F. SORRELLS[1], M. F. PAREDES[2], V. H. PEREZ[5], K. SANDOVAL[2], E. J. HUANG[3], J. GARCIA-VERDUGO[5], A. ALVAREZ-BUYLLA[4]
[1]Dept. of Neurosurg., [2]Neurol., [3]Pathology, [4]Eli and Edythe Broad Ctr. for Regeneration Med.

and Stem Cell Res., Univ. of California San Francisco, San Francisco, CA; [5]Univ. de Valencia, Valencia, Spain

Abstract: The amygdala has an essential role in emotional learning. Abnormal development of this region has been linked to autism, mood and anxiety disorders. The paralaminar amygdala contains multiple nuclei with a high density of cells and is prominent in primates including humans but not present in rodents. It has been hypothesized that the paralaminar nuclei have postnatal plasticity and possibly continued neurogenesis. We studied the development of this region in postmortem and intraoperative human brain samples from fetal, infant, childhood, adolescent, and adult ages. At fetal stages, a high density of young neurons was present in this region of the amygdala, next to the caudal ganglionic eminence. In early postnatal samples (birth to 5 months) we found dividing Ki-67+SOX2+ and Ki-67+OLIG2+ cells within the paralaminar amygdala. After 2 years of age, Ki-67+ cells within this region were rare. Most of the DCX+PSA-NCAM+ neurons within the paralaminar amygdala had round nuclei and multiple long processes and none were Ki-67+. The density of cells within the paralaminar amygdala decreased progressively between 5 months and 77 years of age with a parallel increase in neuropil. The percentage of small DCX+PSA-NCAM+ neurons decreased in this region with age whereas the percentage of large mature NeuN+DCX- neurons increased with age. Interestingly, some small neurons in this region continued to express DCX and PSA-NCAM at 67 and 77 years. Although Ki-67+ cells were rare in the paralaminar amygdala after 2 years of age, DCX+PSA-NCAM+ neurons were observed in all ages studied. This protracted neuronal maturation in the human paralaminar amygdala may be a substrate for plasticity and emotional development in children and adults.

Disclosures: S.F. Sorrells: None. **M.F. Paredes:** None. **V.H. Perez:** None. **K. Sandoval:** None. **E.J. Huang:** None. **J. Garcia-Verdugo:** None. **A. Alvarez-Buylla:** None.

Poster

643. Development of Motor, Sensory, and Limbic Systems: Limbic System

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 643.05/D39

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

Support: NIDA R01DA020140

Title: Dbx1 and Foxp2 dependent formation of the social brain

Authors: *M. J. HERRERO[1], M. GOODRICH[1], J. E. LISCHINSKY[2], A. FOLCARELLI[1], S. SETHI[1], T. SASAKI[1], C. LAZARSKI[1], Y. IMAMURA[3], L. WANG[1], N. SMITH[1], K. HASHIMOTO-TORII[1], J. G. CORBIN[1]
[1]Children's Natl. Med. Ctr., Washington, DC; [2]Smilow Res. Ctr., New York Univ. Med. Ctr.,

New York, NY; [3]Penn State Col. of Medicine. Genome Sci. and Bioinformatics Core, State College, PA

Abstract: The Medial Amygdala (MeA) regulates innate and social behaviors involved in reproduction and defense, essential for survival and the preservation of the species. These behaviors are largely hardwired across species. Here, we are investigating the developmental programs for establishment of innate behavioral circuits, focusing on MeA formation and function. Our previous results showed that different embryonic progenitor pools of cells contributing to the developing MeA can be identified by the non overlapping expression of the transcription factors *Dbx1*, *Foxp2* and *Otp* (Hirata et al., 2009; Carney et al., 2010; Lischinsky et al., 2017). We further found that the embryonic identity of these progenitor populations predicted neuronal identity and innate behavioral activation patterns in adult mice. We are currently exploring the identity of Foxp2 and Dbx1 cell subpopulations across developmental time and in males and females and the mechanisms by which they may regulate innate behaviors. Using FACs sorting and RNA-seq of Foxp2 and Dbx1 positive cells in the MeA at different embryonic stages in mice, we identified differential sets of co-expressing genes. We further find that these developmentally defined subpopulations respond to different neuromodulators and neurohormones. We are further investigating social and innate behaviors in Foxp2 mutant mice. Thus, Foxp2 and Dbx1 neuronal subpopulations in the amygdala may activate different biological pathways to regulate social and innate behaviors, which may also shed light on understanding amygdala-linked developmental disorders such as autism.

Disclosures: M.J. Herrero: None. **M. Goodrich:** None. **J.E. Lischinsky:** None. **A. Folcarelli:** None. **S. Sethi:** None. **T. Sasaki:** None. **C. Lazarski:** None. **Y. Imamura:** None. **L. Wang:** None. **N. Smith:** None. **K. Hashimoto-Torii:** None. **J.G. Corbin:** None.

Poster

643. Development of Motor, Sensory, and Limbic Systems: Limbic System

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 643.06/D40

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

Support: NIH grant HD077623
NIH grant HD079969
NIH grant MH078105-01S1
NIH grant MH091645
NIH grant MH086633
NIH grant U54 HD079124
NIH grant MH100029

Title: Social status and an obesogenic diet affect amygdala, hippocampus and prefrontal cortex development in infant and juvenile macaques

Authors: *M. H. KYLE[1,2], A. KALDAS[1], M. PINCUS[1,2], J. GODFREY[1,2], Z. KOVAKS-BALINT[2], E. MORIN[2,1], L. LI[1], B. R. HOWELL[3], M. STYNER[4], K. ETHUN[2], M. E. WILSON[1,2], M. SANCHEZ[1,2,5]
[1]Emory Univ., Atlanta, GA; [2]Yerkes Natl. Primate Res. Ctr., Atlanta, GA; [3]Univ. of Minnesota, Inst. of Child Develop., Minneapolis, MN; [4]Univ. of North Carolina, Chapel Hill, NC; [5]Ctr. for Behavioral Neurosci., Atlanta, GA

Abstract: Chronic psychosocial stress is associated with psychopathology in children and comorbid with consumption of highly caloric diets that pose a cumulative risk factor for obesity. It is not well understood, though, how neurobehavioral alterations caused by social stress emerge during development and interact with other risk factors, such as obesogenic diets. Here we examined the potential synergistic impact of social stress and an obesogenic diet on infant and juvenile brain development longitudinally and the biological mechanisms involved, using a translational macaque model of social subordination stress. Thirty-eight socially-housed rhesus monkey mother-infant pairs (n=19 dominant (DOM), n=19 subordinate (SUB)) were randomly assigned to either a low-calorie diet (LCD) condition, or had access to both LCD and high-calorie diet (HCD) from birth (Choice). Food intake was recorded continually using automatic feeders and radio-frequency identification (RFID) chips implanted in subjects' wrists. Brain structural MRI data was collected during infancy (2 wks, 6 mo) and in the juvenile period (16 mo). Morning plasma and hair cortisol were analyzed at the same ages to examine stress- and diet-induced activations of neuroendocrine stress systems.
At both 6 and 16 mo, subjects with access to the obesogenic diet showed greater cumulative Kilocalorie consumption and larger overall brain (ICV) volumes, which by 16 months was driven by increases in both white matter and gray matter, but not CSF, volumes. Interestingly, higher Kcal consumption did not predict bigger brain volumes, suggesting that the differences between the Choice and LCD juveniles may be better explained by qualitative differences in the nutrient composition between both diets.
Regarding the effects of social status, by 6 months SUB animals had larger amygdala and hippocampus volumes and these effects persisted at 16 mo, suggesting that early neurodevelopmental effects of social subordination are already detected during infancy and are long-lasting. The only SUB effects detected in prefrontal cortex were smaller CSF volumes at 16 mo.
With respect to cortisol concentrations, animals in the Choice diet condition showed higher levels than those in the LCD condition at 6 mo, which predicted larger right amygdala volumes. Ongoing analysis of the 2-wk data will provide a baseline from which to further examine the longitudinal volumetric effects of diet and social status during development.
These findings suggest that exposure to social subordination and obesogenic diets early in life impacts primate infant structural brain development, resulting in region-specific, not synergistic effects.

Disclosures: M.H. Kyle: None. **A. Kaldas:** None. **M. Pincus:** None. **J. Godfrey:** None. **Z. Kovaks-Balint:** None. **E. Morin:** None. **L. Li:** None. **B.R. Howell:** None. **M. Styner:** None. **K. Ethun:** None. **M.E. Wilson:** None. **M. Sanchez:** None.

Poster

643. Development of Motor, Sensory, and Limbic Systems: Limbic System

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 643.07/D41

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

Support: K01 MH108761
R03HD090308

Title: Amygdala nuclei composition across adolescence using a high-resolution probabilistic atlas

Authors: *C. E. CAMPBELL[1], A. F. MEZHER[1], J. TYSZKA[2], W. M. PAULI[3], B. J. NAGEL[4], M. M. HERTING[1]
[1]USC, Los Angeles, CA; [2]Biol., [3]Caltech, Pasadena, CA; [4]Psychiatry & Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: The amygdala is a hormone receptor dense heterogeneous structure that functionally connects to the striatum, hippocampus, and prefrontal cortex to regulate affective emotion and cognitive function. Current non-invasive studies are trying to understand the relative volume of theses nuclei and the role each play in the amygdaloid complex. The goal of this study was to examine how age, sex, body mass index (BMI), and pubertal stage relates to the relative volume fraction (RVF) of 9 nuclei regions of interest (ROIs) in the amygdala. Whole-brain T1-weighted magnetic resonance imaging scans were acquired on typically developing youths (N=438), age 10-17 years. Probabilistic amygdala labels were generated per hemisphere for each subject, using a new in vivo high-resolution amygdala atlas (CIT168). Probabilistic volumes were calculated, and RVF to total amygdala volume were computed for each ROI. Generalized additive models were used to assess how age, sex, BMI, pubertal stage, and their interactions were associated with amygdala composition. They were corrected for multiple comparisons (Bonferroni $p < 0.0027$). Results showed that females have a larger proportion of their amygdala dedicated to the left central nucleus (CEN) and bilaterally to the amygdalostriatal transition area (ASTA) (R^2 = 4.64-9.71%). In addition, males show bilaterally larger basolateral ventral and paralaminar (BLVPL) subdivision and amygdala transition areas (ATA) (R^2 = 9.35-13.8%) at age 10, but sex differences converge at age 17. Associations with BMI and pubertal stage were observed in select regions, but did not survive multiple comparison corrections. The ASTA projects to the striatum and may be involved with emotional motor reflexes, whereas the adjacent CEN is a primary recipient of internal amygdala connections and - projects to the brainstem, bed nucleus

of the stria terminalis and hypothalamus, to regulate autonomic responses to emotional stimuli. Our finding of a larger CEN in females is consistent with previous research showing females to have a greater physiological response to negative stimuli than males. After receiving afferents from the lateral nucleus and hippocampus, the BLVPL gradually merges with the periamygdaloid cortex (included in the ATA ROI). Moreover, the number of immature neurons in the PL increases with age across postnatal development and is hypothesized to be involved in fear learning. Thus, more research is needed to determine if the current BLVPL and ATA findings may relate to the development of other emotional regulation processes, such as the functional coupling of the amygdala and medial prefrontal cortex that also begins to develop around age 10.

Disclosures: C.E. Campbell: None. **A.F. Mezher:** None. **J. Tyszka:** None. **W.M. Pauli:** None. **B.J. Nagel:** None. **M.M. Herting:** None.

Poster

643. Development of Motor, Sensory, and Limbic Systems: Limbic System

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 643.08/D42

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

Support: NIH Grant K01 MH108761
NIH Grant K23 HD084735
Abell Foundation

Title: Structural differences in amygdalae nuclei in children with classical congenital hyperplasia

Authors: *M. M. HERTING[1], M. CANALES[1], A. MEZHER[1], M. PARKER[2], M. E. GEFFNER[3], M. S. KIM[3]
[1]USC, Los Angeles, CA; [2]Stanford Univ., Palo Alto, CA; [3]Pediatric Endocrinol., Children's Hosp. Los Angeles, Los Angeles, CA

Abstract: Naturally occurring clinical neuroendocrine conditions are vital in bridging knowledge between animal models and healthy humans regarding the role of hormones in amygdala development. Classical Congenital Adrenal Hyperplasia due to 21-hydroxylase deficiency (CAH) is a primary adrenal disorder in which children cannot make adequate amounts of cortisol and aldosterone, yielding excess testosterone during fetal development. Previous research suggests that, compared to matched controls, children with CAH have smaller total amygdalae volume. Although the amygdala is comprised of multiple nuclei with heterogeneous functions and distinct histology, it remains unknown which amygdalae nuclei are distinctly altered in CAH affected youth. The aim of the current study was to examine group differences in

amygdala subnuclei in 9 children with classical CAH (4 female, age 10.62±1.44) compared to 10 age- and sex-matched controls (3 female, age 10.36±1.82). Using T1 and T2 3D structural MRI scans, FreeSurfer v6.0 and amygdala segmentation module were used to quantify total amygdala volumes, as well as volumes of bilateral nuclei including the lateral nucleus, basal nucleus, accessory basal nucleus, anterior amygdaloid area, medial nucleus, cortical nucleus, cortico-amygdaloid transition, and paralaminar nucleus. ANCOVAs were used to examine group and hemisphere differences in total amygdala volumes, while controlling for intracranial volume (ICV). A linear mixed effect model was then performed to investigate group differences in nuclei, with subject as the random factor and controlling for ICV. A significantly smaller total amygdala volume was seen in CAH patients compared to controls [F (1/16)=10.37, p=0.005; partial eta^2=0.23], as well as group differences in amygdala subregions (Likelihood Ratio=34.26, p=0.0001), with CAH children having significantly smaller basal (t=2.88, p=0.0045) and lateral (t=3.45, p=0.0008) nuclei. This study not only replicates previous findings of smaller total amygdala volumes in children with CAH vs controls, but also extends these findings to suggest that basal and lateral nuclei of the amygdalae are smaller in CAH children. Together, the basal and lateral subregions are known to be vital to acquisition and extinction of emotional learning, and thus, may be related to reported alterations in amygdala activity and greater internalizing and externalizing problems in children with CAH. Ongoing research is examining how these structural differences may be associated with hormone imbalances inherent to CAH and/or its glucocorticoid treatment.

Disclosures: M.M. Herting: None. **M. Canales:** None. **A. Mezher:** None. **M. Parker:** None. **M.E. Geffner:** None. **M.S. Kim:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.01/D43

Topic: A.09. Adolescent Development

Title: For adolescent rats, periodic environmental enrichment affects hippocampal c-FOS expression evoked by an acute enriching experience

Authors: *M. PAVELKA[1], S. L. SANTIAGO[2], P. M. CLAYTON[2], E. B. TURNER[2], M. R. WOOD[2], C. T. FENNELL[2], M. C. ZRULL[2]
[1]Psychology & Cell/Molecular Biol., [2]Psychology, Appalachian State Univ., Boone, NC

Abstract: The opportunity for unsupervised interaction with novel objects and same-sex conspecifics in a unique setting, which is often known as environmental enrichment (EE), can have a lasting impact on brain and behavior. More specifically, EE can alter neural activity across hippocampal formation (HF) circuits affecting spatial learning and memory as well as

promoting other informal learning and memory consolidation. We investigated the extent of evoked activity among HF neurons following periodic and/or acute EE exposure in adolescent rats. Twelve Long-Evans rats were exposed to periodic EE between postnatal days (pnd) 25 and 48 and 12 controls were not. During 90-min, daily EE sessions, same-sex enriched rats were placed into enclosures with ramps, platforms, and objects, which were changed each day. Control rats were not enriched but were handled, and all rats lived in same-sized, same-sex groups. Prior to sacrifice on pnd 49, 6 enriched (EE+EE) and 6 control (No+EE) rats experienced a final, acute EE session and other rats did not (EE+No, No+No, n=6 each). Brain tissue was processed using floating section immunohistochemistry to visualize the neural activity marker c-FOS, and activated neurons were quantified in HF regions using digital microscopy and stereological technique. For rats without EE history, a final, acute EE exposure produced more c-FOS+ neurons in dentate gyrus (DG, +103%), a major input region of the HF, internal processing regions, CA3 (+172%), CA2 (+136%), and CA1 (+183%), and in subiculum (Sub, +164%), a major output region of the HF (all $p<.02$). Periodic EE exposure lessened the effect of an acute EE session on evoked neural activity: DG, -17%, CA3, -43%, CA2, -47%, CA1, -64%, and Sub, -41% (all $p<.02$ except DG, $p>.30$). HF neural activity did not differ between rats with and without periodic EE exposure without a final EE session. The data suggest a history of EE experiences does not necessarily alter input available to the HF, via DG activation, during an acute enriching experience. However, periodic EE during adolescence does appear to reduce activation evoked by acute EE as neural signal moves sequentially through the HF. While periodic enrichment during adolescence may or may not habituate animals to novelty, it may make processing of current information by the HF more efficient and impact other opportunities that require learning and memory formation

Disclosures: M. Pavelka: None. **S.L. Santiago:** None. **P.M. Clayton:** None. **E.B. Turner:** None. **M.R. Wood:** None. **C.T. Fennell:** None. **M.C. Zrull:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.02/D44

Topic: A.09. Adolescent Development

Title: For adolescent rats, acute, but not periodic, environmental enrichment affects c-FOS expression in the amygdala

Authors: *C. FENNELL[1], C. A. PEGGS[2], C. E. GAILLARD[3], A. PEREZ[2], S. L. SANTIAGO[2], M. C. ZRULL[2]
[2]Psychology, [3]Interdisciplinary Studies, [1]Appalachian State Univ., Boone, NC

Abstract: Adolescent rats like many mammals, exhibit greater response to novelty and are more likely to engage in risky behavior than adults. For adolescents, environmental enrichment (EE) can provide sensory and motor stimulation as well as opportunity to interact with same-sex conspecifics. An EE experience can evoke behavioral responses to an emotionally arousing situation, which impacts brain development of adolescents who often make decisions based on emotions and novelty. In this study, we examined how periodic and/or acute EE might evoke neural activity in lateral (LA) and basolateral amygdala (BLA) given the relative importance of these structures in learned and unlearned emotional response as well as the evaluation of social cues. Eleven Long-Evans rats were exposed to periodic EE between postnatal days (pnd) 25 and 48 and 10 controls were not. During 90-min, daily EE sessions, same-sex enriched rats were placed into enclosures with ramps, platforms, and objects, which were changed each day. Control rats were not enriched but were handled, and all rats lived in same-sized, same-sex groups. Prior to sacrifice on pnd 49, 6 enriched (EE+EE) and 5 control (No+EE) rats experienced a final, acute EE session and other rats did not (EE+No, No+No, n=5 each). Brain tissue was processed using floating section immunohistochemistry to visualize the neural activity marker c-FOS, and activated neurons were quantified in LA and BLA using digital microscopy and stereological technique. Regardless of periodic EE history, an acute EE session evoked 68% more c-FOS+ neurons in LA and 40% more c-FOS+ neurons in BLA of rats than observed in brains of animals without a final acute EE experience (both $p<.05$). For rats not experiencing a final EE exposure (i.e., EE+No vs. No+No), a history of periodic EE did not produce differences in neural activation in LA or BLA (both $p>.25$). More evoked activity was observed in posterior BLA (pBLA, 70%) than anterior BLA (aBLA, 30%) in all groups except the EE+EE group in which about 50% of c-FOS+ neurons were observed in both pBLA to aBLA. As expected, the data suggest that novelty exposure and emotional response elicited through an EE experience enhances amygdala activity as compared to a baseline. The greater discrepancy between EE-evoked and baseline activation of LA neurons in comparison to BLA neurons may be due to the former's role as the primary target for converging amygdala inputs and acquisition of emotional memory in comparison to the output and behavior-directing role of BLA. Finally, less evoked activity in BLA may also reflect the social behavior inherent to the enriching experience provided in this study.

Disclosures: C. Fennell: None. **C.A. Peggs:** None. **C.E. Gaillard:** None. **A. Perez:** None. **S.L. Santiago:** None. **M.C. Zrull:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.03/D45

Topic: A.09. Adolescent Development

Support: ETSU School of Graduate Studies

Title: Epigenetic transmission of enhanced response to nicotine in the neonatal quinpirole model of schizophrenia

Authors: *W. D. GILL[1], M. J. CHANDLEY[2], L. J. HERNANDEZ[3], W. S. WHICKER[1], C. L. KAESTNER[2], K. C. BURGESS[2], R. W. BROWN[2]
[2]Biomed. Sci., [3]Psychology, [1]East Tennessee State Univ., Johnson City, TN

Abstract: Schizophrenia is a neurological disorder found in approximately 1% of the population. It is estimated that as many as 88% of individuals diagnosed which schizophrenia smoke tobacco, a rate which is increased compared to the general population. Delineation of the biomolecular mechanisms which result in a higher propensity for smoking in vulnerable population may lead to new treatment options. This study investigated the effects of nicotine in an epigenetic transmission model of schizophrenia. Rats were ip administered quinpirole (dopamine D2/D3 agonist) from postnatal days (P)1-21, which results in an increase of D2 receptor sensitivity, and this rodent model has been established to demonstrate face, content, and predictive validity towards schizophrenia. These neonatally treated rats were then bred to produce pups which were not neonatally treated to investigate whether schizophrenia-like symptoms, such as enhanced responding to nicotine, would be transmitted to the untreated offspring of the quinpirole-treated parents. To examine the effects of nicotine in this f1 generation, the rats that were the offspring of animals neonatally treated with quinpirole were behaviorally tested on either a nicotine behavioral sensitization or a nicotine conditioned place preference (CPP) paradigm during adolescence. Following behavioral testing, brain tissue was analyzed for brain-derived neurotrophic factor (BDNF) in the nucleus accubmens, a brain area that is critical to dopaminergic activity that underlies behavioral sensitization and CPP. Additionally, PCR was performed to examine genetic expression of rgs9, a protein that regulates D2 signaling, in the nucleus accumbens. Results revealed that these offspring demonstrated a heightened behavioral sensitization to nicotine, enhanced CPP to nicotine as well as increased accumbal BDNF protein and altered expression of accumbal rgs9 RNA following nicotine administration if at least one parent rat was neonatally treated with quinpirole. These results show that the offspring of rats neonatally treated with quinpirole likely have altered dopaminergic systems in the brain which may indicate a vulnerability to addiction.

Disclosures: W.D. Gill: None. **M.J. Chandley:** None. **L.J. Hernandez:** None. **W.S. Whicker:** None. **C.L. Kaestner:** None. **K.C. Burgess:** None. **R.W. Brown:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.04/D46

Topic: A.09. Adolescent Development

Support: P2D Bioscience

Title: Tumor necrosis factor-alpha modulation results in alleviation of prepulse inhibition deficits and reduction in microglial cell activation produced by neonatal polyinosinic:polycytidylic acid treatment in rats

Authors: *H. W. SHELTON[1], W. D. GILL[1], K. C. BURGESS[1], P. GABBITA[2], R. W. BROWN[1]
[1]Dept. of Biomed. Sci., East Tennessee State Univ., Johnson City, TN; [2]P2D Biosci., Blue Ash, OH

Abstract: Schizophrenia (SZ) is a debilitating neurocognitive disorder that is treated through the use of antipsychotic medications. However, antipsychotic treatment leads to severe dose-dependent side effects. Therefore, there is a need for new adjunctive drugs that reduce the required effective dose of antipsychotics. Previous studies have shown increased neuroinflammation localized in the prefrontal cortex (PFC) and hippocampus (HPC) in individuals diagnosed with SZ. This is largely due to the interaction the pro-inflammatory cytokine tumor necrosis factor-alpha (TNFα) and microglia, which are resident central nervous system defense cells. The purpose of this study was to evaluate a novel small molecule TNFα modulator for improving behavioral deficits and decreasing neuroinflammation in the polyinosinic:polycytidylic acid (Poly I:C) rodent model of SZ. Poly I:C is an immunostimulant that mimics infection in humans, and neonatal infection during pregnancy has been shown to increase the prevalence of SZ later in life. Groups were neonatally treated with saline or Poly I:C (2 mg/kg) from postnatal day (P)5-7 and administered control diet or compound (10 mg/kg) in the diet from (P)30 until (P)67. During adolescence (P)45-46 and in adulthood (P)60-67, rats were behaviorally tested on auditory sensorimotor gating as measured through prepulse inhibition (PPI). Importantly, results revealed that in both adolescence and adulthood, Poly I:C resulted in PPI deficits, and treatment with the TNF modulator significantly improved PPI performance. After (P)67, animals were sacrificed and microglial activation via IBA-1 was evaluated by immunohistochemistry (IHC). Brain tissue was analyzed using confocal microscopy, and images were quantified using NIH ImageJ software. Of the three parameters of analysis, (cell count, sampled cell body fluorescence, and overall image fluorescence) microglia activation in the Neonatal Poly I:C/TNFα group was significantly reduced and was similar to controls when compared to Neonatal Poly I:C/Control group. These results indicate our TNF modulator is successful in improving known behavioral deficits and reducing neuroinflammation associated with SZ and provides a novel pharmacotherapy for the treatment of SZ.

Disclosures: H.W. Shelton: None. **W.D. Gill:** None. **K.C. Burgess:** None. **P. Gabbita:** None. **R.W. Brown:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.05/D47

Topic: A.09. Adolescent Development

Support: 2017-18 Spring Undergraduate Research Grant

Title: Establishing a model of post-traumatic stress disorder in adolescent rats

Authors: *E. WRIGHT[1], M. RUYLE[2], J. MERCADO[2], B. CHELINE[2], T. E. KOELTZOW[1]
[1]Psychology, [2]Bradley Univ., Peoria, IL

Abstract: Diagnostic criteria for Post-traumatic Stress Disorder (PTSD) in adolescents emphasize the need to better understand the behavioral and physiological impact that trauma might elicit during development. The single prolonged stress (SPS) rat model of PTSD reliably produces an enhanced fear response to traumatic cues and disrupted cortisol regulation in adult rats similar to that typically observed in humans with PTSD (Wang et al., 2008; Knox et al., 2012). The purpose of the present study was to determine the long-term impact of SPS (n=10) on adolescent (postnatal day 32-35), male, Sprague Dawley rats compared to controls (n=4). A second aim of the present experiments is to identify individual differences that may confer predict vulnerability to the effects of SPS. Dependent variables included spontaneous locomotor activity as well as responses to an open field (OF), black/white chamber (BW), and an elevated plus maze (EPM).

Data indicate that exposure to SPS elicited persistent alterations in the behavior of adolescent rats (n=10) compared to controls (n=4). The SPS rats tended to exhibit hyperactivity compared to controls in locomotor activity measures 2 weeks post-SPS, as indicated by RMANOVA analysis of total ambulations during a one-hour test (F (1,12) = 0.840, p = 0.19; Cohen's d = 1.27). Similar trends were observed in SPS rats when tested 4 weeks later (F (1,12) = 0.20, p = 0.20; Cohen's d = 0.47). The results of the behavioral anxiety data were more complex. For example, center time in the OF tended to be lower among SPS rats (F (1,12) = 1.25, p = 0.14; Cohen's d = 0.77) when tested two weeks post-inductions, and this trend was present 4 weeks later (F (1,12) = 0.069, p = 0.069; Cohen's d = 0.74). By contrast, no meaningful trends were observed in the BW chamber in terms of black time 2 weeks post-SPS (F (1,12) = 0.429, *n.s*; Cohen's d = 0.37), but when tested 4 weeks later, SPS rats exhibited a strong preference to the black side compared to controls (F (1,12) = 2.740, p = 0.052; Cohen's d = 0.93). Finally, when exposed to the EPM, SPS rats exhibited statistically significant hypoactivity compared to control rats in terms of open arm entries 2 weeks post-SPS (F (1,12) = 4.578, p = 0.027; Cohen's d = 1.3). At 4 weeks post-SPS, a similar trend was observed (F (1,12) = 2.954, p = 0.056; Cohen's d = 0.86). Despite the limited sample size, these results indicate that adolescent rats may be highly susceptible to stress.

On-going research aims to validate these preliminary findings with additional subjects and to identify potential variables that can predict risk versus resilience to the long-term consequences of SPS.

Disclosures: E. Wright: None. **M. Ruyle:** None. **J. Mercado:** None. **B. Cheline:** None. **T.E. Koeltzow:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.06/D48

Topic: A.09. Adolescent Development

Title: Single Prolonged Stress elicits robust behavioral effects in adolescent Wistar Kyoto rats

Authors: M. T. RUYLE, E. B. WRIGHT, J. A. MERCADO, B. C. CHELINE, *T. E. KOELTZOW
Psychology Dept, Bradley Univ., Peoria, IL

Abstract: The single prolonged stress (SPS) model has been utilized in recent years to produce key features of Post-traumatic Stress Disorder (PTSD) in rats. For example, SPS has been reported to reliably produce enhanced fear responses to traumatic cues and disrupted cortisol regulation in adult rats similar to that typically observed in humans with PTSD (Wang et al., 2008; Knox et al., 2012). A key feature of PTSD is that not everyone that is exposed to trauma develops symptoms, indicating that individual differences may serve as a biomarker for vulnerability. Wistar Kyoto (WKY) rats are an inbred strain that have been suggested to be at risk for a variety of affective disorders, including depression and anxiety. The purpose of the present study was to determine whether male, adolescent (postnatal day 33-35) WKY are differentially sensitive to the effects of SPS compared to Sprague-Dawley rats. In addition, a second objective of the current study was to assess the impact of SPS 24 hours after induction in order to determine whether individual differences present shortly after SPS are sufficient to predict long-term consequences to SPS. Dependent variables included spontaneous locomotor activity as well as responses to an open field (OF), black/white chamber (BW), and an elevated plus maze (EPM). Adolescent WKY rats (n=6) were subjected to SPS (two hours of restraint stress, 20 minutes of forced swim, and CO2-induced loss of consciousness) or served as controls (n=12). 24 hours after SPS, rats were subjected to a one-hour locomotor activity test. RMANOVA with one between-groups factor (SPS vs Control) and 12 levels of the within groups factor (5 minute intervals) revealed a statistically significant main effect of condition ($F_{(1,14)} = 6.28$, $p = 0.023$), and a statistically significant Time x Condition interaction ($F_{(11,176)} = 3.07$, $p = 0.001$). These data indicate that exposure to SPS elicits robust hypoactivity inn WKY 24 hours after SPS induction. Ongoing research seeks to determine the potential persistence of these

effects in adulthood, the effect size relative to Sprague-Dawley rats (e.g., see Wright et al., 2018), and to identify behavioral features that may predict individual differences in the magnitude of responses.

Disclosures: M.T. Ruyle: None. **E.B. Wright:** None. **J.A. Mercado:** None. **B.C. Cheline:** None. **T.E. Koeltzow:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.07/D49

Topic: A.09. Adolescent Development

Support: NIH Grant SPN01233

Title: Adolescent ketamine pre-exposure does not alter cocaine preference in adult female mice

Authors: *I. GARCIA[1], A. R. ZAVALA[2], S. D. IÑIGUEZ[1]
[1]Psychology, Univ. of Texas at El Paso, El Paso, TX; [2]Psychology, California State Univ., Long Beach, CA

Abstract: Major Depressive Disorder (MDD) is a prevalent illness that affects females at a higher rate than their male counterparts. Unfortunately, close to 60% of MDD patients do not receive treatment, and when they do, nearly half of them are unresponsive to traditional antidepressants, like fluoxetine. As such, alternative pharmaceutical treatments for MDD are being explored, particularly for juvenile patients - given that the first incidence of MDD is usually reported during this period of development. Recently, ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has shown promising antidepressant efficacy in adolescent treatment-resistant MDD patients. Nevertheless, the possible long-term effects of ketamine exposure during early development have not been assessed. Although there has been some progress in breaching our understanding of how ketamine works by using preclinical models, a limitation of this approach is that most of this work has been done using males as subjects. Thus, we examined whether exposure to ketamine during adolescence results in long-lasting changes in sensitivity to the rewarding properties of cocaine in adulthood using female C57BL/6 mice. Specifically, mice received either ketamine (20 mg/kg) or saline (VEH) for 15 consecutive days during adolescence (Postnatal Day [PD] 35-49). Twenty-one days after ketamine exposure, once mice reached adulthood (PD70), we assessed their behavioral responsivity to cocaine (0, 5, 7.5 mg/kg) using the conditioned place preference (CPP) test. Our results show that adult female mice spent significantly higher time in the cocaine-paired side, as a function of cocaine dose ($p<0.05$). However, juvenile ketamine pre-exposure during adolescence did not influence the magnitude of preference for environments previously paired

with the stimulant, when compared to VEH pre-treated controls, at the same doses of cocaine ($p>0.05$, respectively). Together, our findings suggest that exposure to ketamine during adolescence does not alter sensitivity to the rewarding properties of cocaine in adulthood, in female C57BL/6 mice.

Disclosures: I. Garcia: None. **A.R. Zavala:** None. **S.D. Iñiguez:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.08/D50

Topic: A.09. Adolescent Development

Support: Texas A&M College of Liberal Arts

Title: Extracellular-regulated kinase 2 in the lateral habenula regulates reactivity to stress in adolescent male rats

Authors: *L. F. PARISE, O. K. SIAL, A. M. CARDONA, E. L. VIEREGG, P. N. SKANSI, C. BOLAÑOS-GUZMAN
Texas A&M Univ., College Station, TX

Abstract: Approximately 13% of individuals aged 12-17 are diagnosed with major depressive disorder (MDD). Early-life MDD is highly debilitating, andthe World Health Organization reports suicide as a leading cause of death among adolescents and young adults. Althoughtreatments for MDD are available, they are only partially effective, and a large portion of adolescents are non-responsive,suggesting that there is much left to be understood about the underlying neurocircuitry that mediates symptoms of MDD. Stress is a primary factor in precipitating MDD thus necessitating assessment of how it alters neural signaling of mood-related genes during developmental periods prior to adulthood. To this end, adolescent (postnatal day 35) male rats were exposed to 4 weeks of chronic unpredictable stress (CUS), then tested in behavioral assays designed to assess stress-reactivity, and tissue was subsequently collected for biochemical analysis. After CUS exposure, rats were tested in the elevated plus maze (EPM), forced swim test (FST), and for sucrose preference. Stress-exposed rats spent less time in the open arms of the EPM, indicative of an anxiogenic response, while also showing increased total immobility in the FST (i.e., behavioral despair) and had reduced sucrose consumption (i.e., anhedonia). We have previously shown that extracellular regulated kinase 2 (ERK2) activity in mesolimbic structures, such as the ventral tegmental area (VTA), is a key mediator of stress- and antidepressant-responding. The VTA receives regulatory input from the lateral habenula (LHb), however, knowledge of whether ERK2 is regulated in the LHb after stress is lacking. To this end, rt-PCR and western blot were performed, revealing that both mRNA and protein levels of

ERK2 in the LHb were decreased after CUS exposure. To assess whether direct ERK2 modulation could buffer CUS-induced behavioral deficits, naïve adolescent rats received microinfusions of wtERK2, to increase ERK2 expression within the LHb, and then exposed to the EPM and FST. Increasing ERK2 within the LHb promoted more time in the open arms of the EPM and less time immobile in the FST (i.e., antidepressant-like effects). A separate group of CUS-exposed rats received LHb infusions of wtERK2 prior to behavioral testing. Similar to naïve rats, increasing ERK2 within the LHb was sufficient to promote antidepressant-like responses in the EPM and the FST, when compared to the GFP-treated controls. These results suggest that increasing ERK2 in the LHb promotes resilience to stress and can reverse a depressive-like phenotype. Overall these findings highlight the importance of LHb second-messenger signaling in mediating resilience to stress.

Disclosures: L.F. Parise: None. **O.K. Sial:** None. **A.M. Cardona:** None. **E.L. Vieregg:** None. **P.N. Skansi:** None. **C. Bolaños-Guzman:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.09/D51

Topic: A.09. Adolescent Development

Support: SC2Gm109811

Title: Juvenile combination treatment with fluoxetine and aripiprazole does not alter cocaine-seeking behavior in adulthood

Authors: *S. A. CASTILLO[1], A. R. ZAVALA[2], S. D. IÑIGUEZ[3]
[1]Biol. Sci., [2]Psychology, The Univ. of Texas At El Paso, El Paso, TX; [3]California State Univ., Long Beach, CA

Abstract: Major depressive disorder (MDD) is a highly debilitating illness that affects millions of people across the globe. Interestingly, the first reported incidence of MDD occurs during the adolescence stage of development. Because fluoxetine (FLX) is the only antidepressant medication approved by the Food and Drug Administration (FDA) for the treatment of pediatric MDD, the prescriptions rates of this antidepressant are very high within populations younger than 20 years of age. Unfortunately, FLX does not alleviate MDD symptoms in most patients - with close to 50% being resistant to this pharmacotherapeutic treatment. An alternative approach for treatment resistant-MDD is the prescription of FLX in combination with the atypical antipsychotic aripiprazole (ARI). This is surprising, given that the long-term consequences of this combination treatment (FLX+ARI) have not been thoroughly assessed at either the clinical or preclinical level. Thus, the purpose of this study is to examine for potential long-term

consequences of juvenile combination therapy with FLX+ARI on sensitivity to drugs of abuse in adulthood. To achieve this, adolescent (postnatal day [PD] 35) male C57BL/6 mice were administered with either vehicle (DMSO) or FLX (10 mg/kg) with aripiprazole (0.03 mg/kg) for 15 consecutive days (PD35-49). Twenty-one days later, once the mice reached adulthood (PD70), they were tested for cocaine (5 mg/kg) sensitivity using the conditioned place preference test (CPP). The results of this experiment show that when tested in adulthood, animals pretreated with FLX+ARI during adolescence do not differ in the time spent in the cocaine-paired side when compared to VEH-treated controls. Together, our results suggest that no long-lasting reward-related deficits become apparent in male C57BL/6 mice exposed to FLX+ARI during the adolescent stage of development.

Disclosures: A.R. Zavala: None. **S.D. Iñiguez:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.10/E1

Topic: A.09. Adolescent Development

Support: NIH Grant UL1GM118979
NIH Grant TL4GM118980
NIH Grant RL5GM118978

Title: Neonatal caffeine does not disrupt locomotor activity in adolescence but attenuates the expression of locomotor sensitization to methylphenidate

Authors: *R. MEHTA, B. SORTMAN, C. GERAGHTY, C. J. RICHARD, A. R. ZAVALA
California State University, Long Beach, Long Beach, CA

Abstract: Chronic neonatal caffeine exposure, depending on the age of initial treatment, has been shown to produce hyperactivity in adolescent and adult rats exposed to a novel environment. This caffeine-induced hyperactivity has only been demonstrated in rats that are pretreated during postnatal days (PDs) 7-11, but not if given between PD 13-17. The present experiment studied whether neonatal caffeine exposure produces hyperactivity and whether neonatal caffeine exposure affects the development of methylphenidate sensitization in adolescent rats. Rats were pretreated with either saline or caffeine (20 mg/kg) on PD 7 for seven consecutive days (i.e., PD 7-13) and horizontal locomotor activity was assessed from PD 25-28. For five consecutive days thereafter, rats were pretreated with saline or methylphenidate (2.5 or 5 mg/kg). A methylphenidate challenge was then conducted on PD 34, during which rats received saline or methylphenidate (2.5 mg/kg). Unlike previous findings, neonatal caffeine exposure did not produce hyperactivity in adolescent rats. However, the development of methylphenidate

sensitization was attenuated in rats that received neonatal caffeine. Specifically, neonatal caffeine pretreated male rats did not increase their locomotor response across the five days of pretreatment with methylphenidate (5.0 mg/kg) compared to controls, which exhibited an increase in locomotor activity across the five methylphenidate pretreatment days. Moreover, during the methylphenidate challenge, neonatal caffeine pretreated female rats exhibited an attenuated sensitized response when challenged with methylphenidate (2.5 mg/kg) compared to controls. These findings suggest that neonatal caffeine exposure during PD 7-13 may have a long-lasting disruption of dopaminergic systems that persist into adolescence.

Disclosures: R. Mehta: None. **B. Sortman:** None. **C. Geraghty:** None. **C.J. Richard:** None. **A.R. Zavala:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.11/E2

Topic: A.09. Adolescent Development

Support: NIH Grant UL1GM118979
NIH Grant TL4GM118980
NIH Grant RL5GM118978

Title: The effects of early-life ketamine administration on the rewarding effects of alcohol in male and female adolescent sprague dawley rats

Authors: *D. FRANCO[1], E. NUNEZ LARIOS[1], R. A. CABRERA[1], S. D. INIGUEZ[2], A. R. ZAVALA[1]
[1]Psychology, California State Univ. Long Beach, Long Beach, CA; [2]Psychology, Univ. of Texas at El Paso, El Paso, TX

Abstract: Although the prevalence of major depressive episodes (MDEs) in juvenile populations has significantly increased in recent years, treatment with fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has failed to adequately manage depressive symptoms in more than one-third of children and adolescents. As a result, there is a critical need for novel therapeutic agents with the ability to effectively and efficiently treat depression. Recently, a single low-dose of ketamine, a non-competitive NMDA receptor antagonist, has been shown to produce rapid and effective antidepressant effects in clinical and preclinical models. However, the long-term effects of early and prolonged ketamine administration in juvenile populations are unclear. Specifically, because ketamine is also a drug of abuse, early ketamine exposure may inadvertently alter the developing brain reward systems, and thereby increase the abuse potential of other drugs of abuse (e.g., alcohol). Thus, we examined whether early ketamine administration

increases the rewarding effects of alcohol in adolescent rats using the conditioned place preference (CPP) paradigm, a validated animal model of reward. Periadolescent male and female Sprague-Dawley rats received daily ketamine injections from postnatal day (PD) 21-30. One day after the last ketamine injection, rats were assessed for alcohol-induced CPP on PD 31 using a 10-day CPP procedure. On days 1 and 10, rats were tested for their preconditioning and postconditioning place preference, respectively, for 15-minute sessions. On days 3-8, rats were conditioned 15 minutes a day with either alcohol (0.0, 0.125, 0.5, 2.0 g/kg) or saline on alternating days. Results show that early ketamine administration modulates the rewarding effects of alcohol in adolescence. Specifically, the degree of alcohol-induced CPP is shaped by previous ketamine exposure. Overall, the results demonstrate that early life ketamine administration alters the rewarding properties of alcohol during adolescence. Consequently, ketamine use in clinical trials involving juvenile populations should be carefully evaluated.

Disclosures: D. Franco: None. **E. Nunez Larios:** None. **R.A. Cabrera:** None. **S.D. Iniguez:** None. **A.R. Zavala:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.12/E3

Topic: A.09. Adolescent Development

Support: Texas A&M College of Liberal Arts

Title: Social stress during adolescence followed by western-style diet leads to physiological dysregulation, depressive phenotype, and decreases in reward sensitivity in adulthood

Authors: *O. K. SIAL, L. F. PARISE, P. N. SKANSI, A. M. CARDONA, E. L. VIEREGG, T. GNECCO, C. A. BOLAÑOS-GUZMÁN
Psychology, Texas A&M Univ., College Station, TX

Abstract: The prevalence of major depressive disorders (MDD) and obesity in adolescence has steadily increased over the last decade. This comorbidity has been reported by clinicians and a relationship between depression- and anxiety-like states with cardiac and metabolic dysfunction has also been demonstrated in rodents. Conversely, western-style high fat diet (HFD) has been linked to the development of metabolic syndrome and mood dysregulation. While much has been elucidated about the neural basis of depression and obesity, how they converge is unknown. It is unclear whether chronic stress induces physiological and neurobiological changes associated with metabolic dysfunction or vice versa, thus understanding potential mechanism(s) and/or directionality is paramount. To this end, adolescent (postnatal day [PD]30) male C57bl/6J mice were exposed to HFD either before or after chronic social defeat stress (CSDS), and then tested

for behavioral and physiological dysregulation. Mice were given free access to HFD for 14 days (PD30-44) prior to CSDS exposure (10 days; 10 minutes/day), and subsequently tested for sucrose preference. Mice did not show changes in caloric intake or total body weight regardless of diet. However, those in the HFD condition showed a significant decreased in preference for sucrose (i.e., increased anhedonia) when compared to the NC-exposed mice. A separate group was given access to HFD alone for 4 weeks and tested in the conditioned place preference (CPP) paradigm to assess for changes in drug reward. Mice pretreated with HFD did not develop preference to the side compartment paired with morphine (1.0 mg/kg), which promoted CPP in the NC-exposed mice. Combined, these results demonstrate that pre-exposure to HFD blunts responses to both natural and drug reward. A separate group of mice was exposed to CSDS before the introduction of the HFD. There was no change in calories consumed, but a significant increase in body weight after only 10 days of HFD was observed. After 1 month of NC or HFD consumption, the mice were re-tested for social avoidance. The NC-exposed mice showed significant recovery in social interaction whereas the HFD-exposed mice showed profound social avoidance suggesting that pre-exposure to stress alters the physiological response to HFD and promotes a depression-like phenotype. Together, these findings indicate that exposure to HFD during adolescence blunts reward sensitivity, and that stress exposure followed by consumption of HFD induces neurobiological changes that lead to physiological and mood related deficits which could lead to the development of maladaptive behaviors and negative health outcomes in adulthood.

Disclosures: O.K. Sial: None. **L.F. Parise:** None. **P.N. Skansi:** None. **A.M. Cardona:** None. **E.L. Vieregg:** None. **T. Gnecco:** None. **C.A. Bolaños-Guzmán:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.13/E4

Topic: A.09. Adolescent Development

Support: SC2GM109811

Title: Fluoxetine pre-exposure decreases cocaine and sucrose preference in female mice

Authors: *F. J. FLORES RAMIREZ[1], M. ARENIVAR[1], A. THEMANN[1], M. RODRIGUEZ[1], O. LIRA[1], J. PRECIADO-PINA[1], A. R. ZAVALA[2], S. D. IÑIGUEZ[1]
[1]Psychology, Univ. of Texas At El Paso, El Paso, TX; [2]Psychology, California State Univ., Long Beach, CA

Abstract: Preclinical literature indicates that exposure to antidepressant medications, during early stages of development, results in long-term altered behavioral responses to drugs of abuse

(Iñiguez et al., 2015, Sci Rep, 5:15009). However, to date, these studies have been conducted in male subjects primarily. This is surprising, given that females, when compared to males, are more likely to be diagnosed with mood-related disorders, and thus, be prescribed with antidepressants. Therefore, the objective of this study is to assess whether exposure to the selective serotonin reuptake inhibitor fluoxetine (FLX) results in long-lasting alterations in sensitivity to the rewarding properties of cocaine and sucrose, using female mice as a model system. To do this, adolescent (postnatal day [PD]-35) and adult (PD70) female C57BL/6 mice were exposed to FLX (in their drinking water, 250 mg/l) for 15 consecutive days. Twenty-one days later (PD70+ and PD105+, respectively), mice were assessed on behavioral responsivity to cocaine (0, 2.5, 5, 7.5 mg/kg) using the conditioned place preference paradigm, or their sensitivity to a 1% sucrose solution using the 2-bottle choice test. Our results indicate that female mice pre-exposed to FLX during adolescence or adulthood displayed reliable conditioning to the cocaine-paired compartment, in a dose-dependent manner. However, when compared to respective age-matched controls, antidepressant pre-exposure decreased the magnitude of conditioning at the 5 ($p<0.05$, $R^2= 0.21$) and 7.5 mg/kg ($p<0.05$, $R^2= 0.51$) cocaine doses. Similarly, independent of age of antidepressant pretreatment, FLX-pretreated mice also displayed a decrease in sucrose preference ($p<0.05$, $R^2= 0.62$), without altering total liquid intake ($p>0.05$). Collectively, our results suggest that exposure to FLX, in adolescent and adult female C57BL/6 mice, leads to prolonged decreases in sensitivity to the rewarding properties of both drug- and natural-rewards. This data further highlight the need for investigations assessing the potential enduring neurobiological side effects that may arise later in life, as a result of antidepressant exposure, in a sex dependent manner.

Disclosures: F.J. Flores Ramirez: None. **M. Arenivar:** None. **A. Themann:** None. **M. Rodriguez:** None. **O. Lira:** None. **J. Preciado-Pina:** None. **A.R. Zavala:** None. **S.D. Iñiguez:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.14/E5

Topic: A.09. Adolescent Development

Support: Texas A&M College of Liberal Arts

Title: Alprazolam exposure during adolescence dysregulates reward sensitivty and second messenger signalingin adulthood

Authors: A. M. CARDONA, L. F. PARISE, O. K. SIAL, E. L. VIEREGG, J. P. ROZOFSKY, *C. A. BOLANOS-GUZMAN
Psychological and Brain Sci., Texas A&M Univ., College Station, TX

Abstract: Benzodiazepines are prescribed widely as anxiolytics, hypnotics, muscle relaxants, and anticonvulsants. However, their utility is limited by unwanted side effects such as abuse liability and the potential for dependence. Benzodiazepine-related emergency room visits have increased in the US within the past two decades and despite concerns surrounding their use, there has been a substantial increase in benzodiazepine's prescription rate. Benzodiazepines are commonly abused concurrently with opioids, resulting in greater psychopathology and increased comorbidity. There is evidence of increased use and abuse of benzodiazepines during adolescence, yet most available neurobiological evidence has been based on studies using adult organisms. This study was designed to investigate whether exposure to alprazolam during adolescence also potentiates the behavioral and biochemical effects of opiates such as morphine. Adolescent C57BL/6J male mice were treated with alprazolam (0.25, 0.5 and 1.0 mg/kg)or saline, once daily from postnatal days 35-49. Changes in behavioral responsiveness to morphine (0.5, 1.0 and 5.0 mg/kg), using the conditioned place preference paradigm (CPP), and gene expression changes within the ventral tegmental area (VTA), using qPCR,were assessed both 24 h and one-month after the end of drug treatment.Our results show that pretreatment with alprazolam during adolescence potentiates the effects of morphine as measured in the CPP paradigm: the alprazolam pre-treated mice developed strong preference to the compartment paired with a threshold dose of morphine (0.5 mg/kg), and this effect was still present a month after alprazolam exposure. We then measured whether extracellular signal-regulated kinase 1/2 (ERK)-signaling would be affected by alprazolam pretreatment, given ERK's role in mediating drug-induced behaviors. Preliminary results show a decrease in GSK3β and ERK2 gene expression when compared to controls 24 h after alprazolam treatment. Ongoing studies are currently assessing expression of other transcription factors such as CREB, BDNF cFos, and zif268.Overall, these findings suggest that exposure to alprazolam during adolescence potentiates the rewarding effects of opiates such as morphine, and that alprazolam exposure during this period result in persistent changes of ERK-signaling within the VTA, a brain region implicated in both drug-reward and mood-related disorders, in adulthood.

Disclosures: A.M. Cardona: None. **L.F. Parise:** None. **O.K. Sial:** None. **E.L. Vieregg:** None. **J.P. Rozofsky:** None. **C.A. Bolanos-Guzman:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.15/E6

Topic: A.09. Adolescent Development

Support: NIH Grant UL1GM118979
NIH Grant TL4GM118980
NIH Grant RL5GM118978

Title: The role of glucagon-like peptide 1 receptors on the rewarding effects of oxycodone in male and female adolescent rats

Authors: *Y. C. BROWN, C. J. RICHARDS, A. R. ZAVALA
Psychology, California State University, Long Beach, Long Beach, CA

Abstract: Available treatments for drugs of abuse are limited. Preclinical studies show activation of Glucagon-like peptide-1 receptors (GLP-1R) reduces the rewarding effects of alcohol and cocaine through the modulation of dopamine release in the mesolimbic pathway, suggesting GLP-1R may be a good pharmacotherapeutic target. However, the role of GLP-1R in modulating opioid reward has not been examined. This study is examining whether Exendin-4 (EX-4), a GLP-1R agonist, will reduce the rewarding effects of oxycodone, an opioid receptor agonist, in adolescent male and female adolescent rats. The rewarding effects of Oxycodone were assessed using the Conditioned Place Preference (CPP) paradigm-an animal model of reward. CPP involved a 10-day procedure. On days 1 and 10, rats were tested for their preconditioning and postconditioning place preference, respectively, for 15-minute sessions. On days 3-8, rats were conditioned 30 minutes a day with either oxycodone (0.0, 0.01, 0.1, 1.0, or 9.0 mg/kg) or saline on alternating days. During oxycodone conditioning sessions, rats were pretreated with EX-4 (2.4 ug/kg) or saline 10 min before being conditioned with oxycodone. Results indicated that Ex-4 attenuated oxycodone-induced CPP in male and female adolescent rats. Overall, this study adds to a growing body of literature that suggests GLP-1R may be a target in reducing the abuse of various drugs of abuse.

Disclosures: C.J. Richards: None. **A.R. Zavala:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.16/E7

Topic: A.09. Adolescent Development

Support: NIH Grant R15MH100585

Title: Differential consequences of post-natal and post-weaning environment on the relative playfulness of F344 and Lewis rats

Authors: *S. M. SIVIY, C. M. CAMPBELL, J. A. GENTES, L. GUSTAFSON
Dept Psychol, Gettysburg Col., Gettysburg, PA

Abstract: Previous work from our lab has shown that the Fischer 344 (F344) rat is consistently less playful than other strains and while the overall level of playfulness in F344 and Lewis (LEW) rats is fairly resistant to cross-fostering, how this urge is titrated by motivational factors

in the two strains may be differentially sensitive to early postnatal experiences (*Physiol Behav*, 2017, 116, 147). To further understand the dynamic interplay between genotype and postnatal experiences, we assessed the effects of neonatal handling on rough-and-tumble play in LEW and F344 rats when allowed to play with a standard Sprague-Dawley (SD) partner. Handled litters experienced brief daily periods (15 min) of separation during the first 2 postnatal weeks and then remained undisturbed until weaning at 21 days of age. When play was assessed after weaning and compared to rats from non-handled control litters, F344 rats were less playful overall but handled LEW and F344 rats were both more likely to respond to playful nape contacts with complete rotations to supine, suggesting that handling increased playful responsiveness to a comparable extent in both strains. SD rats paired with handled inbred rats responded by directing more nape contacts to the inbred partner than those paired with non-handled rats, perhaps reflecting the contagious nature of play, but only when assessed after 4 hours of isolation when overall playfulness was at a sub-maximal level. This was, in turn, countered with more nape contacts by handled LEW rats but not by handled F344 rats. These data suggest that early postnatal handling may be having a differential impact on how motivational state modulates the ebb and flow of a play bout in F344 and LEW rats. In a separate experiment, the consequences of differential housing after weaning were assessed by housing F344 and LEW rats with either 2 rats of the same strain or 2 SD rats immediately upon weaning. When play was assessed between 35 and 40 days of age F344 rats solicited less play than LEW rats and play solicitation in both strains was unaffected by cross-housing. While playful responsiveness in LEW rats was unaffected by housing condition, F344 rats housed with SD rats for 2 weeks were more likely to respond to playful solicitations with a complete rotation than those housed with other F344 rats and did not differ from the playful responsiveness of LEW rats. Taken together, these data suggest that different components of social play, such as playful solicitation and responsiveness, may be differentially sensitive to pre- and post-weaning social experiences and the exact impact on play may depend somewhat on the genetic platform that these experiences are acting on.

Disclosures: S.M. Siviy: None. **C.M. Campbell:** None. **J.A. Gentes:** None. **L. Gustafson:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.17/E8

Topic: A.09. Adolescent Development

Title: Individual differences in social play behaviour in rats: How do they affect adult social behaviour and reward sensitivity?

Authors: *M. ACHTERBERG, H. M. B. LESSCHER, L. J. M. J. VANDERSCHUREN
Fac. of Vet. Med., Utrecht, Netherlands

Abstract: Social play behaviour is a characteristic form of social behaviour displayed by the young of many mammalian species, including rats and humans. Being a rewarding activity, the performance of social play depends on its pleasurable and motivational properties. Importantly, social play behaviour is modulated through neural systems that also mediate the rewarding and motivational effects of other rewards such as food, sex and substances of abuse. Social play behaviour is thought to have an important role in socio-emotional and cognitive development. This is supported by experiments in which rats were deprived of social play, by housing them in isolation during the period in which this behaviour is most abundant (postnatal day 21 to 42). This play deprivation makes rats unable to respond appropriately to social and cognitive challenges in adulthood. Next to that, play-deprivation leads to enhanced sensitivity for cocaine self-administration, amphetamine and alcohol place preference and alcohol consumption in adulthood. Since play-deprivation profoundly affects brain and behaviour, individual differences in playfulness may have long-term implications as well. To investigate this, we characterized young rats on the expression of social play behaviour and subsequently tested them on their motivation to play, adult social behaviour, impulsivity and operant responding for sucrose and alcohol. In addition, expression of relevant genes was assessed in brain regions involved in social play, reward processes and executive functioning. Preliminary data indicate that individual differences in social play expression predict the motivation for social play as well as reward sensitivity and gene expression.

Disclosures: M. Achterberg: None. **H.M.B. Lesscher:** None. **L.J.M.J. Vanderschuren:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.18/E9

Topic: A.09. Adolescent Development

Support: NIH

Title: Nicotinic driven adolescent shift of local/long-range input balance onto a prefrontal top-down projection establishes adult attentional control

Authors: E. NABEL[1], M. DEMARS[3], Y. GARKUN[4], K. CARO[5], J. SHORT[6], G. TACCHERI[6], S. IM[5], S. LOPEZ[5], K. J. NORMAN[9], M. SADAHIRO[2], H. KOIKE[5], M. G. BAXTER[7], *H. MORISHITA[8]
[2]Psychiatry, Neuroscience, Opthalmology, Friedman Brain Inst., [1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]Psychiatry, [4]Icahn Sch. of Med. at Mount Sinai, New York, NY; [5]Icahn

Sch. of Med. at Mount Sinai, New york, NY; [6]Icahn Sch. of Med. at Mount Sinai, new york, NY; [7]Dept Neurosci., [8]Psychiatry, Neuroscience, Ophthalmology, Icahn Sch. of Med. at Mount Sinai, New York, NY; [9]Neurosci., Icahn Sch. of Med., New York, NY

Abstract: Neuromodulation plays two separate essential roles at different ages: during early fetal age in cell development, and later in adulthood in altering neural dynamics and plasticity. Neuromodulatory tone is present in the brain between these two developmental stages, but its role during adolescence, when circuit formation occurs, is less extensively explored. The prefrontal cortex (PFC) experiences protracted development that extends through adolescence during which inputs from local PFC and distal brain regions are integrated into circuits that interface sensory and cognitive information to support complex cognitive behaviors. To what extent neuromodulatory mechanism contributes to this late developmental process is not known. Here, we examine the role of neuromodulation in circuit development of evolutionarily conserved PFC top-down neurons projecting from dorsal anterior cingulated cortex and secondary motor cortex to primary visual cortex (PFC->VIS) in mice. Rabies input mapping identified robust basal forebrain cholinergic inputs onto top-down PFC->VIS projection neurons established by adolescence. However, electrophysiological recording reveals decreased nicotinic ACh response in adult PFC->VIS projection neurons compared to adolescence, as the projection neurons undergo a shift in cell-autonomous suppression of nicotinic signaling through expression of a nicotinic brake, Lynx1. Bidirectional viral manipulations of Lynx1 expression within PFC->VIS projection neurons revealed that adolescent, and not adult, Lynx1 expression is necessary and sufficient to develop adult attentional performance on the 5 choice serial reaction time task. Exploration of Lynx1-dependent changes in connectivity onto PFC->VIS projection neurons revealed that Lynx1 facilitates a selective reduction in heightened local connectivity onto top-down projections through the suppression of excessive dendritic spine formation that shifts the balance of local/long-range inputs in adulthood. Our study reveals that adolescent cell-autonomous molecular control over nicotinic neuromodulatory transmission is essential for prefrontal top-down projection neurons to shift the connectivity balance of local and long-range inputs to establish adult attentional control.

Disclosures: E. Nabel: None. **M. Demars:** None. **Y. Garkun:** None. **K. Caro:** None. **J. Short:** None. **G. Taccheri:** None. **S. Im:** None. **S. Lopez:** None. **K.J. Norman:** None. **M. Sadahiro:** None. **H. Koike:** None. **M.G. Baxter:** None. **H. Morishita:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.19/E10

Topic: A.09. Adolescent Development

Support: NIH

Title: Prefrontal parvalbumin Interneurons require juvenile social experience to establish adult social behavior

Authors: *L. BICKS[1], K. YAMAMURO[3], M. FLANIGAN[5], E. K. LUCAS[6], H. KOIKE[3], M. S. PENG[6], J. M. KIM[1], Z. DONG[1], R. L. CLEM[4], S. J. RUSSO[1], S. AKBARIAN[7], H. MORISHITA[2]
[2]Psychiatry, Neuroscience, Ophthalmology, [1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Neurosci., [3]Mount Sinai Sch. of Med., New York, NY; [6]Neurosci., [7]Psychiatry, [5]Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Social isolation during developmental critical windows could be highly detrimental to proper functioning of mature prefrontal cortex (PFC) and establishment of appropriate adult behaviors. However, the specific circuits that undergo social experience-dependent maturation to regulate social behavior development are poorly understood. Here we show that juvenile social isolation in mice leads to reduced intrinsic excitability and input drives of adult parvalbumin-positive interneurons (PVIs) in medial PFC (mPFC), suggesting juvenile social experience is required for their proper activation in adulthood. *In vivo* imaging of mPFC-PVI activity by fiber photometry demonstrated that adult mPFC-PVIs are preferentially activated by social signals. Acute chemogenetic suppression of mPFC-PVI activity revealed that normal social behavior requires physiological mPFC-PVI activity. Conversely, chemogenetic restoration of mPFC-PVIs activity in the adult animal selectively rescued juvenile isolation-induced social deficits but not increased anxiety. Therefore, PVI development in the juvenile mPFC is critically linked to long-term impacts on social behavior.

Disclosures: L. Bicks: None. **K. Yamamuro:** None. **M. Flanigan:** None. **E.K. Lucas:** None. **H. Koike:** None. **M.S. Peng:** None. **J.M. Kim:** None. **Z. Dong:** None. **R.L. Clem:** None. **S.J. Russo:** None. **S. Akbarian:** None. **H. Morishita:** None.

Poster

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.20/E11

Topic: A.09. Adolescent Development

Support: NIH R21 NS105119

Title: Prefrontal top-down cortico-cortical projection in control of attentional behavior

Authors: *K. J. NORMAN[1], H. KOIKE[2], S. LOPEZ[2], E. NABEL[5], M. FLANIGAN[5], Y. GARKUN[2], Z. DONG[2], M. DEMARS[3], M. G. BAXTER[6], S. J. RUSSO[2], H. MORISHITA[4]

[1]Neurosci., Icahn Sch. of Med., New York, NY; [3]Psychiatry, [4]Psychiatry, Neuroscience, Ophthalmology, [2]Icahn Sch. of Med. at Mount Sinai, New York, NY; [5]Icahn Sch. of Med. At Mount Sinai, New York, NY; [6]Dept Neurosci., Mount Sinai Sch. Med., New York, NY

Abstract: Attention is a goal-directed cognitive process that facilitates the detection of task-relevant sensory stimuli from our dynamic environment. Attention deficits are frequently observed in several psychiatric disorders; including autism spectrum disorders, schizophrenia, and depression, yet the underlying neural circuits that regulate attentional behavior are not well understood. Across species, previous studies have demonstrated that the frontal cortex—particularly the anterior cingulate cortex (ACC) — contributes to "top-down" control of sensory processing in the visual cortex (VIS). Here, we aim to investigate the contribution of these evolutionarily conserved, long-range ACC->VIS projecting neurons in top-down control of visual attention behavior. We achieve this by integrating cutting-edge circuit-based techniques to monitor and manipulate selective top-down neural activity in mice performing freely moving attention behavior with a translational automated touchscreen system. Our study has shown that selective chemogenetic suppression of ACC->VIS projections impairs attentional performance in the 5-choice serial reaction time task without disrupting additional detectable readouts of decision-making capacity, motivational state, motor activation, impulsivity, and compulsivity. *In vivo* calcium imaging of projection-specific top-down neurons using fiber photometry in behaving mice points to a key role of top-down projections in integrating sustained attention and visual processing. Direct optogenetic modulation of the projection further reveals temporal- and frequency-dependent bidirectional change in attentional performance. Collectively, our data demonstrate that long-range frontal-sensory projections are a key enactor of top-down control of attentional behavior. Our findings may provide circuit-based insight into the pathophysiology and neuromodulation intervention strategies for impaired visual attention in neuropsychiatric disorders. Our ongoing study aims to rescue attention deficits in mice with risk genes for neurodevelopmental disorders through the modulation of frontal-sensory projections.# equal first authors (Norman and Koike)

Disclosures: K.J. Norman: None. **H. Koike:** 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

644. Adolescent Development: Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 644.21/E12

Topic: A.09. Adolescent Development

Title: Selective sub-populations of prefrontal excitatory and inhibitory neurons require juvenile social experience to establish adult excitability

Authors: *K. YAMAMURO[1,2,3,4,5], L. K. BICKS[1,2,3,4,5], Y. GARKUN[1,2,3,4,5], H. MORISHITA[1,2,3,4,5]
[1]Dept. of Psychiatry, Icahn Sch. of Med., New York, NY; [2]Dept. of Neuroscience, Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Dept. of Ophthalmology, Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Mindich Child Hlth. and Develop. Institute, Icahn Sch. of Med. at Mount Sinai, New York, NY; [5]Friedman Brain Institute, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Juvenile social isolation (jSI) during a two-week window (p21-35), but not a later window leads to decreased social investigation in adult mice, suggesting the juvenile period as a critical period for adult social behavior. However, the specific circuitry that is vulnerable to jSI is unknown. We assessed the effect of jSI in adult medial prefrontal cortex (mPFC) including anterior cingulate cortex and prelimbic cortex by patch clamp recordings from fluorescently labeled excitatory and inhibitory neurons of jSI and group housed (GH) mice. We found that jSI causes a lasting reduction in intrinsic excitability in adult mPFC neurons projecting to midline limbic thalamus but not in neurons projecting to Nucleus accumbens, nor to contralateral mPFC. We next patched from mPFC inhibitory neurons in mice whose Parvalbumin-interneurons (PVI) or Somatostatin-interneurons (SSTI) are fluorescently labeled. SSTI are further divided into three subtypes based on firing patterns, low-threshold spike (LTS), quasi-fast spiking (QFS) and adapting (AD). Of note, layer II/III SSTI overwhelmingly are of the AD subtype. We found that adult mPFC SSTI-QFS neurons showed comparable excitability in jSI and GH mice. In striking contrast, adult mPFC SSTI-AD neurons both in upper and lower cortical layers and PVI show markedly decreased excitability after jSI compared to GH. In contrast, adult LTS-type SSTIs from jSI mice showed elevated intrinsic excitability. Collectively, our study demonstrates that selective sub-population of excitatory and inhibitory neurons in mPFC require proper juvenile social experience to establish normal intrinsic excitability in adulthood. Given that social processing deficits are a common dimension of many neurodevelopmental and psychiatric disorders, identification of the specific circuits sensitive to experience-dependent modulation will point toward therapeutic targets that allow amelioration of social deficits shared across of range of disorders.

Disclosures: K. Yamamuro: None. **L.K. Bicks:** None. **Y. Garkun:** None. **H. Morishita:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.01/E13

Topic: A.09. Adolescent Development

Support: UCI Institutional Support for FML

Title: Developmental and sex differences in kappa opioid receptor activity in limbic brain areas

Authors: *S. J. CROSS[1], D. BE[1], C. CARMONA[1], F. M. LESLIE[1,2]
[1]Anat. & Neurobio., [2]Pharmacol., Univ. of California Irvine, Irvine, CA

Abstract: The kappa opioid receptor (KOR) and its endogenous ligand, dynorphin, are widely distributed in the brain, including in regions involved in motivation and reward, executive function, and stress responsiveness. Activation of KORs has been shown to induce a compensatory decrease in reward state that is thought to be mediated by inhibition of dopaminergic and serotonergic signaling. However, KOR function and KOR modulation of drug-associated behaviors often differs between males and females. Furthermore, although present early in development, increasing evidence suggests that KORs undergo functional maturation during adolescence, a sensitive developmental period associated with major reorganization of brain regions critical for reward processing. Our lab has previously shown that the reinforcing properties of concurrent nicotine and alcohol (Nic+EtOH) are enhanced in adolescent males, but not females or adult males, likely due to differential activation of KORs. To test the hypothesis that KOR activity differs across development and by sex to differentially modulate Nic+EtOH reinforcement, brain tissue from drug naïve adult and adolescent rats was processed for U69,593-stimulated [^{35}S]GTPγS binding to determine functional KOR activity. KOR activity was found to differ across age and sex, with adolescent males having greater KOR activity in the ventral tegmental area (VTA) and median raphe (MR) compared to adult males. Adolescent males also showed greater KOR activity than adolescent females in the basolateral amygdala (BLA). In contrast, adult females had higher KOR activity than adult males in all subregions of the amygdala, while adolescents did not differ between sexes. These data demonstrate that while males show developmental decreases in KOR function in the VTA and MR, females show increases in KOR function in the amygdala. Our findings highlight the sex-dependent functional maturation of KORs in limbic brain areas important for reward, reinforcement, and stress responses.

Disclosures: S.J. Cross: None. **D. Be:** None. **C. Carmona:** None. **F.M. Leslie:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.02/E14

Topic: A.09. Adolescent Development

Support: Intramural Research Program of the National Institute of Mental Health, National Institutes of Health

Title: Sex and pubertal stage: Effects on the awakening cortisol response

Authors: *P. E. MARTINEZ[1], J. J. HUGGINS[1], E. D. ROBINSON[3], K. D. THOMPSON[1], K. M. REDING[2], S.-M. WEI[2], L. A. SCHENKEL[1], S. M. BRADY[5], J. A. YANOVSKI[5], K. F. BERMAN[6], S. J. SOLDIN[4], L. K. NIEMAN[8], P. J. SCHMIDT[7]
[1]Behavioral Endocrinol. Br., [2]Clin. and Translational Neurosci. Br., NIH/National Inst. of Mental Hlth., Bethesda, MD; [3]Nursing, [4]Dept. of Lab. Med., NIH, Bethesda, MD; [5]Section on Growth and Obesity, NIH/Eunice Kennedy Shriver Natl. Inst. of Child Hlth. and Human Develop., Bethesda, MD; [6]Clin. and Translational Neurosci. Br., [7]Behavioral Endocrinol. Br., NIH/National Inst. of Mental Hlth., Bethesda, MD; [8]Section on Translational Endocrinol., NIH/National Inst. of Diabetes and Digestive and Kidney Dis., Bethesda, MD

Abstract: Abnormalities of hypothalamic-pituitary-adrenal (HPA) axis are frequent accompaniments of mood and anxiety disorders. Adolescence (and puberty) are associated with both an increased onset of mood/anxiety disorders, as well as the emergence of sex differences in the risk for these conditions (i.e., a 2-fold increased life-time risk in women compared with men). Finally, sex differences in HPA axis response to a range of stressors are documented in both rodents and humans. We employed the awakening cortisol response (ACR) to evaluate the HPA axis in a sample of normally-developing pre and post pubertal children. We studied 60 prepubertal children (23 girls, 37 boys) and 29 post pubertal children (13 girls,16 boys). Pubertal stage (PS) was assessed by a trained clinician: in boys based on testicular volume (TV) using the Prader orchidometer; in girls based on breast development. All children (and 1st degree relatives) were free of any past/current psychiatric disorder (as determined by structured diagnostic interview); all children were medically well, medication free, had a BMI within the 15th -85th percentile, normal bone age, and normal IQs. ACR tests were analyzed from the first visit in the prepubertal cohort and from the PS 5 visit in the older cohort. Salivary cortisol was measured by chemiluminescent enzyme immunoassay on Siemens Immullite1000 analyzer. The ACR area under the curve (AUC) and individual time points (0, 30, 45 and 60 minutes) were analyzed by ANOVAs. In the AUC cortisol there was a significant main effect of sex ($F_{1,88}$=6.0; p=0.02) but no main or interactive effects of PS (p=0.2 and p=0.3, respectively). Similarly, the individual timepoints showed significant main effects of sex (ANOVA-R: $F_{1,88}$=4.2, p=0.04) and time ($F_{1,87}$=19.4, p<.001), but no main effects of PS, nor any between-subjects interactive effects (p=ns, all comparisons). In summary, we found no effects of pubertal stage on the ACR and that sex differences in the ACR occurred independently of pubertal stage. Therefore, our findings suggest (albeit preliminarily) that sex differences in HPA axis appear prior to gonadarche. These findings are analogous to previous adult data from our group (Roca, et al. 2005) in which sex differences in HPA axis responsivity were observed after men and women were made hypogonadal by leuprolide treatment, such that hypogonadal men developed greater ACTH and cortisol responses to either exercise or corticotropin releasing hormone (CRH) stimulation compared with women.

Disclosures: P.E. Martinez: None. **J.J. Huggins:** None. **E.D. Robinson:** None. **K.D. Thompson:** None. **K.M. Reding:** None. **S. Wei:** None. **L.A. Schenkel:** None. **S.M. Brady:** None. **J.A. Yanovski:** None. **K.F. Berman:** None. **S.J. Soldin:** None. **L.K. Nieman:** 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.; Received grant support from HRA Pharma for the development of metyrapone. **P.J. Schmidt:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.03/E15

Topic: A.09. Adolescent Development

Title: A novel genomic approach predicts brain volume and behavior in healthy children based on DCC co-expression network

Authors: *A. MORGUNOVA[1], K. J. O'DONNELL[2,5,3,7], M. J. MEANEY[2,5,3,7,8], P. P. SILVEIRA[3,5,2], C. A. FLORES[2,4,6]
[1]McGill Univ., Verdun, QC, Canada; [2]Dept. of Psychiatry, Fac. of Med., [3]Sackler Program for Epigenetics & Psychobiology, [4]Neurol. and Neurosurg., McGill Univ., Montreal, QC, Canada; [5]Ludmer Ctr. for Neuroinformatics and Mental Hlth., [6]Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada; [7]Child and Brain Develop. Program, Canadian Inst. for Advanced Res. (CIFAR), Toronto, ON, Canada; [8]Agency for Science, Technol. and Res. (A*STAR), Singapore Inst. for Clin. Sci., Singapore, Singapore

Abstract: The *DCC* receptor directs growing axons to appropriate targets and plays a critical role in prefrontal cortex (PFC) maturation in adolescence. *DCC* haploinsufficiency in humans leads to altered mesocorticolimbic connectivity and *DCC* single nucleotide polymorphisms (SNPs) associate with depression and schizophrenia. Here, we created a polygenic score, which takes into account that genes operate in coherent networks, and investigated how variations in genes co-expressed with *DCC* in the PFC are involved in healthy human development. We postulated that genetic variation in the *DCC* gene network will unfold discrete differences in behavior and brain morphology in a cohort of Canadian children (MAVAN project).
Followed from birth to 12 years of age with multiple behavioral measures (n=260; 131 females), 64 of the children (n=64; 33 females) underwent MRI and had genetic data collected (Psychchip/Psycharray). First, we obtained genes highly co-expressed with *DCC*, with brain region (PFC) and age (1.5 to 11 y.o.) specificity, from human postmortem gene expression and genotype databases. Then, we used the gene expression slope coefficient, derived from the GTEx regression model, to weigh the SNPs located in these genes. The polygenic score is thus created

by combining the estimated effects of SNPs for the alleles that each subject carries.
Based on Euclidean matrix of gene expression from postmortem data, we find that genes co-expressed with *DCC* exhibit pronounced clusters of upregulated and downregulated expression during the childhood period. However, this expression pattern dissipates in adolescence, coinciding with the dramatic developmental changes that are ongoing in the PFC during this time. We also find that the *DCC* polygenic score in PFC predicts brain volume in healthy individuals. Children with high polygenic score have significantly smaller brain volumes, when adjusted for age, sex and ethnicity. Furthermore, volumetric thalamus measures are smaller in children with high *DCC* co-expression scores, with substantial variance among boys. Finally, measures of behavioral impulse control reveal that high polygenic score group exhibits lower response inhibition.
Our pioneering study reveals that the differential expression of the prefrontal cortex *DCC* gene network can predict brain volume in healthy children and could serve as a powerful identification of developmental differences and possible vulnerabilities to disorders.

Disclosures: A. Morgunova: None. **K.J. O'Donnell:** None. **M.J. Meaney:** None. **P.P. Silveira:** None. **C.A. Flores:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); National Institute of Drug Abuse.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.04/E16

Topic: A.09. Adolescent Development

Title: Cognitive control networks and related vulnerabilities for alcohol abuse in adolescents with childhood trauma

Authors: S. SILVEIRA[1], K. B. NOONER[3], B. J. NAGEL[4], S. TAPERT[2], M. D. DEBELLIS[5], *J. MISHRA[2]
[1]Psychiatry, Univ. of California San Diego, San Diego, CA; [2]Psychiatry, Univ. of California San Diego, La Jolla, CA; [3]Psychology, Univ. of North Carolina Wilmington, Wilmington, NC; [4]Psychiatry & Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [5]Psychiatry, Duke Univ. Med. Ctr., Chapel Hill, NC

Abstract: Individuals with childhood trauma are vulnerable to adverse life outcomes and show elevated risk for alcohol and substance abuse, which emerges during adolescence. This is also a critical time period when cognitive control, a fundamental cognitive capacity of the human brain that allows us to select and maintain goal-relevant information, while ignoring goal-irrelevant distractions, is developing. Two distinct cognitive control brain networks have previously been identified, the fronto-parietal network (FPN) and the cingulo-opercular network (CON). While

the FPN has been ascribed to enabling moment-to-moment task control, the CON is associated with sustained task control. Notably, CON and FPN are not distinctly segregated during childhood. Adolescence marks the critical period during which the key cognitive control hub in the dorsal anterior cingulate cortex (dACC) segregates from FPN to form the CON. In the current study, we investigate the maturation and segregation of cognitive control brain networks in N = 388 adolescents with varying levels of trauma severity in the multisite NCANDA (National Consortium on Alcohol & Neurodevelopment in Adolescence) cohort. We analyze functional network connectivity using blood oxygen level dependent signal time course correlations of resting state functional magnetic resonance imaging (fMRI) data with the dACC as a seed region of interest. In a regression model, we analyze the relationship between mean functional connectivity network strength from the baseline rs-fMRI scans and childhood trauma scores as measured by the Childhood Trauma Questionnaire-2 (CTQ-2). Trauma-impacted functional network connectivity outcomes are used in a linear mixed effects model to test prediction of variance in binge drinking as measured by the Customary Drinking and Drug Use Record (CDDR) collected at baseline and at 1- and 2-year follow-up assessments. All analyses control for participants' sex, age, socioeconomic status, and study site MRI scanner type (GE vs. Siemens). In line with our preliminary findings, we hypothesize that FPN and CON functional network segregation will be modulated by the severity of trauma. Further, we specifically hypothesize that the maturing functional connectivity of the dACC node that segregates to form the CON, will be hampered by childhood trauma, and that this will predict higher levels of binge drinking. Results from this study will significantly advance the understanding of how functional network development during adolescence contributes to alcohol and substance abuse. This research also has the potential to inform network-targeted therapeutics for individuals with childhood trauma.

Disclosures: S. Silveira: None. **K.B. Nooner:** None. **B.J. Nagel:** None. **S. Tapert:** None. **M.D. Debellis:** None. **J. Mishra:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.05/E17

Topic: A.09. Adolescent Development

Support: CONACYT 1840
CONACYT 628500

Title: Chronic stress in adolescence and its relationship with the development of mood disorders

Authors: *M. A. PEREZ HERNANDEZ[1], A. ESCALANTE-VARELA[4], N. ISMAIL[5], R. SHARMA[5], B. BERNAL-MORALES[2], T. CIBRIAN-LLANDERAL[3]

[2]Inst. de Neuroetologia, [3]CONACYT-Instituto de Neuroetologia, [1]Univ. Veracruzana, Xalapa, Mexico; [4]Inst. Veracruzano de Salud Mental Rafael Velasco Fernandez, Xalapa, Mexico; [5]Sch. of Psychology, Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Introduction. Exposure to stress during critical periods of development can lead to enduring changes in functioning of the brain and body that can impact physical and mental health. **Objective**. Examine the role of chronic stress during puberty on the future development of stress-related psychopathologies such as depression, anxiety and suicidal ideation. **Method**. Observational, retrospective, descriptive and transversal study. In this project, participants were chosen between 18-40 years from Veracruz Institute of Mental Health Doctor Rafael Velasco Fernandez (IVSM) who presented a diagnosis of anxiety, depression and/or presence of suicidal ideation, also a control group was chosen. We applied Beck's anxiety and depression inventories and a questionnaire about the factors associated with chronic stress in adolescence. This project was approved by the ethics and research committee of the IVSM. The statistical analysis included descriptive statistic and chi square test in SPSS program. **Results:** 227 participants, 58% were women and 42% men. The prevalence of moderate or severe anxiety was 48% for women and 41% for men, for moderate or severe depression, it was 30% for women and 24% for men, for suicidal ideation it was 30% for women and 21% for men. We found significant differences ($p \leq 0.05$) in the results of women group who presented moderate and severe anxiety (ANS), moderate and severe depression (DEP), suicidal ideation (SI) and high prevalence of physical variables and the control group. The statistical significant differences for ANS were in the following evaluated symptoms: nausea, diarrhea, back pain, dizziness, headache, weakness, chest pain, shortness of breath, heart palpitations, abuse and type of abuse. The statistical differences for DEP were in nausea, back pain, shortness of breath, heart palpitations and abuse. For SI the statistical significant differences were in dizziness, weakness, chest ache, abuse and type of abuse. We found significant differences ($p \leq 0.05$) in the results of men group who presented moderate and severe anxiety (ANS), moderate and severe depression (DEP) and high prevalence of physical variables and the control group. The statistical significant differences for ANS were in weakness, abuse and type of abuse. The statistical differences for DEP were in headache, chest pain, abuse and type of abuse. **Conclusions**. Chronical stressful experiences in adolescence could have the potential to make a person vulnerable to experiencing endocrine and affective disorders that could harm health.

Disclosures: M.A. Perez Hernandez: None. **A. Escalante-Varela:** None. **N. Ismail:** None. **R. Sharma:** None. **B. Bernal-Morales:** None. **T. Cibrian-Llanderal:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.06/E18

Topic: A.09. Adolescent Development

Support: NIDA: R01DA037911
CIHR: MOP-74709
NSERC: 2982226

Title: Adolescent levels of circulating miR-218 predict susceptibility to chronic social defeat stress in adult mice

Authors: *A. TORRES BERRIO[1,2], A. MORGUNOVA[2], C. FLORES[3]
[1]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Integrated Program in Neurosci., [3]Dept. of Psychiatry, McGill Univ., Montreal, QC, Canada

Abstract: Adolescence is a period of Increased vulnerability to psychiatric disorders including depression. However, there is still the need of discovering novel biomarkers to identify those individuals who are at the highest risk. The microRNA, miR-218, mediates susceptibility to depression by targeting the guidance cue receptor gene, *Dcc* (Deleted in colorectal cancer) in the prefrontal cortex (PFC). Furthermore, circulating levels of miR-218 correlate with depression-like behaviors in adult mice, following the chronic social defeat stress (CSDS) paradigm. Here, we assessed whether (1) the PFC expression pattern of miR-218 and *Dcc* varies across postnatal neurodevelopment, (2) miR-218 expression in blood changes throughout life, and (3) circulating miR-218 during adolescence predicts susceptibility to CSDS in adulthood. We show that miR-218 expression in the PFC increases drastically from early adolescence to adulthood, whereas *Dcc* mRNA expression decreases in the exact opposite manner. In fact, miR-218 and *Dcc* mRNA levels correlate negatively across postnatal life. Circulating miR-218 increases from adolescence onward, paralleling those changes observed in the PFC. Importantly, high circulating levels of miR-218 during adolescence are strongly associated with vulnerability to CSDS in adulthood. In fact, adult susceptible mice display "adult-like levels" of miR-218 in blood during adolescence. Downregulation of miR-218 in the PFC specifically during adolescence prevents vulnerability to CSDS in adulthood. These results show that the pattern of postnatal expression of miR-218 in the PFC is dynamic and reproduced when measured in blood. Furthermore, miR-218 levels in the PFC appear to maintain *Dcc* expression in this region from adolescence to adulthood. We propose that circulating levels of miR-218 might indicate vulnerability to stress throughout life.

Disclosures: A. Torres Berrio: Other; Present address: Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, USA. **A. Morgunova:** None. **C. Flores:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.07/E19

Topic: A.09. Adolescent Development

Support: NIH Grant R01DA037911
NSERC Grant 2982226
CIHR Grant MOP-74709
FRQNT Grant 208332

Title: Environmental cues alter the timing of adolescent neural development in Siberian hamsters

Authors: *D. HOOPS[1], R. F. KYNE[4], A. HE[2], K. C. SCHATZ[5], L. LIN[6], C. FLORES[3], M. J. PAUL[7]
[1]Psychiatry, McGill Univ., Verdun, QC, Canada; [2]McGill Univ., Montreal, QC, Canada; [3]Dept of Psych, McGill Univ., Verdun, QC, Canada; [4]Univ. At Buffalo, Tonawanda, NY; [5]Univ. at Buffalo, Bufallo, NY; [6]Univ. at Buffalo, Buffalo, NY; [7]Psychology, Univ. at Buffalo, SUNY, Buffalo, NY

Abstract: Siberian hamsters (*Phodopus sungorus*) are seasonally-breeders that restrict reproduction to spring and summer, when conditions are favourable for offspring survival. Those born early in the breeding season enter puberty during the summer, while those born late delay puberty over the winter months. Hamsters use changes in day length to detect the time of year, and therefore, summer and winter pubertal phenotypes can be reproduced in the lab by rearing hamsters in long, summer-like photoperiods or short, winter-like photoperiods. We recently found that photoperiod impacts the development of some adolescent behaviours, such as novelty seeking, but not others, such as the transition from juvenile play to adult aggression. In the present experiment, we test whether photoperiod impacts neural changes associated with adolescence. The dopamine innervation to the prefrontal cortex is one of the most striking hallmarks of adolescent development, as axons grow long distances to innervate this region during adolescence. Hamsters were reared under a long or short photoperiod and sacrificed as pre-adolescents, young adults, or old adults. Dopamine innervation to the prefrontal cortex was visualized using immunohistochemistry, and innervation was quantified as the density of dopamine varicosities. Paired testes and uterine weights were recorded to confirm reproductive responsiveness to photoperiod. As expected, puberty, as measured by increases in paired testes and uterine weights, was delayed in short photoperiod-reared hamsters compared to those reared under a long photoperiod. Paralleling sex organ development, dopamine innervation was also delayed in hamsters reared under a short photoperiod. To our knowledge, this is the first demonstration that the timing of the adolescent development of mesocortical dopamine input can be plastic in response to environmental cues. In combination with previous behavioural experiments, this experiment demonstrates how this seasonal-species approach can used to dissect out the neural and endocrine mechanisms that regulate adolescent development.

Disclosures: D. Hoops: None. **R.F. Kyne:** None. **A. He:** None. **K.C. Schatz:** None. **L. Lin:** None. **C. Flores:** None. **M.J. Paul:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.08/E20

Topic: A.09. Adolescent Development

Support: NIH Grant R01DA042595

Title: Cannabinoid exposure in adolescence dysregulates genes that orchestrate dopamine development and enhances cocaine-motivated behavior

Authors: *N. E. ZLEBNIK[1], S. CUESTA[4], S. KUMMER[6], D. NOUEL[4], J. M. WENZEL[2], C. FLORES[5], J. F. CHEER[3]
[2]Anat. & Neurobio., [3]Anat. and Neurobio., [1]Univ. of Maryland Sch. of Med., Baltimore, MD; [5]Dept of Psych, [4]McGill Univ., Verdun, QC, Canada; [6]Univ. of Pompeu Fabra, Barcelona, Spain

Abstract: Initiation of drug use during adolescence is a strong predictor of both the incidence and severity of addiction throughout the lifespan. Among adolescents, marijuana is the most commonly abused illicit drug, and excessive use of cannabinoids in this population is associated with the development of psychiatric conditions, including drug addiction. Adolescence is a critical period for the refinement and organization of neuronal connectivity, especially within the mesocorticolimbic dopamine circuity. We have shown, in male mice, that exposure to high doses of amphetamine in early adolescence (PND21-32) disrupts the development of mesocorticolimbic dopamine connectivity, leading to alterations in cognitive processing in adulthood. Importantly, this effect is mediated by amphetamine-induced downregulation of the guidance cue receptor gene, *Dcc*, in ventral tegmental area (VTA) dopamine neurons. DCC receptors orchestrate the development of the mesocorticolimbic dopamine system in adolescence by determining the spatiotemporal targeting of dopamine axons. Here, we examined whether exposure to the synthetic CB1/2 receptor agonist WIN-55,212-2 (WIN) in adolescence regulates *Dcc* mRNA expression in the VTA and induces, in turn, adult alterations in cocaine-related behaviors and in dopamine function in adulthood. We treated early adolescent mice (PND21-32) with repeated intraperitoneal injections of saline or WIN, using 3 different doses (0.5, 2, 4 mg/kg). Mice received one injection every other day for a total of 5 times. We find that exposure to WIN strongly attenuates *Dcc* mRNA expression in the VTA one week later. Remarkably, exposure to the same WIN regimen in early adolescence results in enhanced cocaine seeking in adulthood as measured using a mouse intravenous self-administration paradigm. We are currently examining phasic dopamine release in brains of adult mice exposed to WIN or saline in adolescence. These findings show that repeated exposure to a CB1/2 receptor agonist in adolescence impacts vulnerability to drug addiction later in life and that *Dcc*-mediated disruption of mesocorticolimbic dopamine maturation might be at play.

Disclosures: N.E. Zlebnik: None. **S. Cuesta:** None. **S. Kummer:** None. **D. Nouel:** None. **J.M. Wenzel:** None. **C. Flores:** None. **J.F. Cheer:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.09/E21

Topic: A.09. Adolescent Development

Title: Effects of adolescent WIN exposure on perineuronal net emergence in PFC

Authors: *E. JACOBS-BRICHFORD[1], H. CHEN[3], A. W. LASEK[2], J. D. ROITMAN[4]
[2]Psychiatry, [1]Univ. of Illinois At Chicago, Chicago, IL; [3]Psychiatry, UIC, Chicago, IL; [4]Psychology, Univ. of Illinois at Chicago, Chicago, IL

Abstract: A hallmark of adolescent brain development is the establishment of a finely-tuned excitatory-inhibitory (E-I) balance in the prefrontal cortex (PFC). This balance, which comes online as inhibitory signaling is refined, helps regulate neuron activity and is essential for the acquisition of cognition in adulthood. In PFC, E-I balance is established over a protracted period of development, with remodeling of inhibitory signaling extending into late adolescence/early adulthood. The brain is particularly vulnerable to environmental insult during this time, including drugs of abuse. Indeed, exposure to cannabis - the most commonly used illicit drug among adolescents - during this time has been linked to memory impairment, increased risk for addiction, and heightened risk of psychosis or schizophrenia in individuals with a predisposition. Cannabis use during adolescence is also known to alter PFC neural activity in adulthood, but little is known about the effects of cannabis on the PFC *during* its development.
To address this gap in our knowledge, we investigated the effect of cannabinoid treatment on the structural development of PFC. Specifically, we examined how exposure to WIN 55, 212-2 (WIN) from postnatal day 35-45 affected the maturation of perineuronal nets (PNNs), lattice-like structures that wrap around cells and regulate their excitability. In the PFC, they are predominantly found on parvalbumin-expressing interneurons (PV), a population of inhibitory cells that develop during adolescence and regulate pyramidal cell excitability. PNN formation is known to be influenced by drug exposure, and we hypothesized that exposure to cannabinoids may disrupt their formation around PV cells, therefore altering the ability of PV cells to regulate pyramidal cell output. We used immunohistochemistry to analyze the fluorescence intensity of two extracellular components of PNNs, brevican and neurocan, as well as *Wisteria floribunda* agglutinin (WFA), a plant lectin that often colocalizes with PNNs. Additionally, we double-labeled brevican, neurocan, and WFA with PV cells in order to determine if any changes in expression are due to a change in the number of cells covered by PNNs or simply a change in intensity of expression.

Disclosures: E. Jacobs-Brichford: None. **H. Chen:** None. **A.W. Lasek:** None. **J.D. Roitman:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.10/E22

Topic: A.09. Adolescent Development

Support: NIH Grant P50AA017823
NIH Grant T32AA025606

Title: Chronic intermittent ethanol exposure produces long-lasting changes in immune function and corticosterone sensitivity when experienced during adolescence, but not in adulthood

Authors: *A. S. VORE, T. M. BARNEY, J. E. MONDELLO, T. DEAK
Binghamton Univ., Binghamton, NY

Abstract: Adolescence represents a time of heightened vulnerability to many of the neurotoxic effects of ethanol, yet previous studies have shown cytokine gene expression was substantially reduced/impaired during early adolescence, regardless of what type of challenge was imposed (LPS or ethanol). Interestingly, adolescent exposure to chronic intermittent ethanol (CIE) led to sexually dimorphic outcomes, with male rats exhibiting impaired cytokine gene expression in adulthood. In contrast, females displayed no alteration in cytokine reactivity and instead exhibited sensitized CORT release to later challenges in adulthood, an effect that was absent in males. The goal of the present study, therefore, was to test whether these sexually dimorphic effects of adolescent CIE were unique to the adolescent period, or a more general response to ethanol that would also be observed in adult CIE-exposed rats. To test this, Sprague Dawley rats were given daily 4.0 g/kg intragastric (i.g.) ethanol exposures for three consecutive days followed by two days of abstinence/withdrawal. This "cycle" was repeated for a total of four "cycles" spanning postnatal day (P) P70-P90 and then left undisturbed for an equivalent amount of time as our prior work in adolescents (~20-30 days). At P110, all rats received a one-hour restraint stress challenge and cytokine gene expression and CORT were measured. Female rats with a history of adolescent CIE displayed increased CORT release 60 minutes into restraint challenge. As expected, restraint increased circulating CORT in both male and female rats, and neither sex showed changes in CORT release as a consequence of adult ethanol history. Although adult female rats with an adult history of CIE displayed significantly reduced IL-1β expression, this difference was not observed in any other target gene examined (IL-6, TNF-α, IκBα). Male rats displayed no effects of adult CIE on any of these targets. These data suggest that our previously documented effects reflect adolescent-specific changes in immune and HPA-axis function, and that adult rats given an identical pattern of binge-like ethanol exposure display

mostly stable cytokine expression in response to restraint challenge later in life. It is perhaps worth noting that adult female rats with a history of i.g. intubations (relative to non-intubated controls) displayed altered basal IL-1 & IκBα expression. This may reflect a unique vulnerability of female rats to procedural stress. These data contribute to a growing body of work demonstrating that the unique sensitivity of adolescents to alcohol use alters immune and neuroimmune sensitivity later in life, even after long periods of abstinence.

Disclosures: A.S. Vore: None. **T.M. Barney:** None. **J.E. Mondello:** None. **T. Deak:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.11/E23

Topic: A.09. Adolescent Development

Support: AA019767
AA011605
AA007573
AA021040
AA020023
AA020024
AA020022

Title: Neuroimmune and epigenetic mechanisms underlying the adolescent binge ethanol-induced loss of basal forebrain cholinergic neurons: Restoration with anti-inflammatory drugs and voluntary exercise

Authors: *R. P. VETRENO[1], J. P. BOHNSACK[2], S. C. PANDEY[3], W. LIU[4], F. T. CREWS[5]
[1]Sch. of Med., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [2]Dept. of Psychiatry, [3]Alcohol Res. Center, Dept Psychiatry, Univ. of Illinois at Chicago, Chicago, IL; [4]Bowles Ctr. for Alcohol Studies, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Prof Pharmacol & Psychiat, Skipper Bowles Ctr. Alcohol, Chapel Hill, NC

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 (P56) into adulthood (P220), an effect that we observed in the post-mortem human alcoholic basal forebrain. However, the mechanism underlying the persistent loss of cholinergic neurons remains to be elucidated. We tested the hypothesis that voluntary exercise and/or anti-inflammatory drug treatment would restore the AIE-induced loss of basal forebrain cholinergic neurons. We report

here that wheel running from P56 (24 hr after the conclusion of AIE) to P95 restored the AIE-induced cholinergic neuropathology as well as the increase of proinflammatory pNF-κB p65 in the adult (P95) basal forebrain. Further, AIE induced dimethylation of H3K9 on both the ChAT and TrkA genes as well as DNA methylation on the ChAT promoter CpG Island, which were reversed with exercise exposure. Exercise also recovered the AIE-induced behavioral flexibility impairments on the Morris water maze in adulthood. Administration of the anti-inflammatory drug indomethacin during AIE blocked the AIE-induced loss of cholinergic markers and concomitant increase of pNF-κB p65. Together, these data implicate a novel neuroplastic process involving neuroimmune and epigenetic mechanisms resulting in the phenotypic loss of basal forebrain cholinergic neurons following AIE. Further, these data reveal that AIE does not cause immediate cholinergic neuron degeneration highlighting the potential for the development of therapeutics. Supported by the NADIA of the NIAAA.

Disclosures: R.P. Vetreno: None. **J.P. Bohnsack:** None. **S.C. Pandey:** None. **W. Liu:** None. **F.T. Crews:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.12/E24

Topic: A.09. Adolescent Development

Support: NIH Grant DA037911
NIH Grant DA041188
CIHR Grant MOP-74709
NSERC 2982226
FRQS

Title: The effects of amphetamine exposure in adolescence on Netrin-1 receptors, dopamine development, and cognitive maturation are sex-specific

Authors: *L. M. REYNOLDS[1,2], S. ISRAEL[1,2], S. CUESTA[2], M. WODZINSKI[2], M. HE[2], C. FORTIN-CLAES[2], C. FLORES[2]
[1]Integrated Program in Neurosci., [2]Psychiatry, McGill Univ., Montréal, QC, Canada

Abstract: Drug use in adolescence increases later vulnerability to addiction. In male mice, repeated exposure to amphetamine (AMPH) during early adolescence downregulates the expression of the Netrin-1 receptor DCC in dopamine neurons, disrupting the development of mesocortical dopamine connectivity and leading to deficits in prefrontal cortex-dependent behaviors that persist into adulthood. However, the effects of this drug regimen on females remain unknown. Here, we treated male and female mice with an intraperitoneal regimen of

AMPH (4 mg/kg, producing peak plasma levels similar to human recreational use) or saline during early adolescence (PND 22±1-31±1). We assessed DCC expression in the ventral tegmental area (VTA) one week after treatment in females, as we have previously in males. In contrast to our previous findings in males, AMPH did not alter VTA DCC expression in female mice one week after treatment, indicating that AMPH exposure regulates VTA DCC expression not only in an age-dependent (Yetnikoff et al; 2007, 2011, 2013), but also in a sex-specific manner. We then measured behavioral inhibition, motivation, and risk-taking-like behavior in separate cohorts of adult male and female mice exposed to the same AMPH or saline regimen in adolescence. When compared to their saline-treated littermates, adult males that were exposed to AMPH during early adolescence showed impairments in behavioral inhibition, increased risk taking-like behavior, and an inability to adapt to changing reward contingencies. However, we observed no behavioral differences between adult females exposed to AMPH or saline in early adolescence. In males, AMPH exposure in early adolescence disrupts the development of mesocortical dopamine connectivity in a *Dcc*-dependent manner. We are currently assessing the effects of the AMPH or saline regimen on dopamine connectivity in females. Our data show that, in male mice, AMPH exposure in early adolescence downregulates VTA DCC expression and leads to cognitive alterations in adulthood that are associated with addiction vulnerability. Strikingly, the exact same AMPH regimen does not lead to these molecular and behavioral changes in female mice.

Disclosures: L.M. Reynolds: None. **S. Israel:** None. **S. Cuesta:** None. **M. Wodzinski:** None. **M. He:** None. **C. Fortin-Claes:** None. **C. Flores:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.13/E25

Topic: A.09. Adolescent Development

Support: NIH Grant 1R01DA037911-01A1
NSERC Grant 2982226

Title: Opposite effects of low versus high doses of amphetamine in adolescence on dopamine development and behavior

Authors: *J. RESTREPO[1,3], S. CUESTA[2,3], L. M. REYNOLDS[1,3], C. POPESCU[1], S. HE[1], C. FORTIN[3], J. EPELBAUM[1], S. SILVESTRIN[3], C. FLORES[2,3]
[1]McGill Univ., Verdun, QC, Canada; [2]Psychiatry, McGill Univ., Montreal, QC, Canada; [3]Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada

Abstract: The guidance cue receptor DCC plays a critical role in the development of the mesocortical dopamine system in adolescence. Furthermore, repeated exposure to an amphetamine regimen of 4 mg/kg (a dose that reaches plasma levels similar to those achieved by abused doses in humans) during early adolescence, induces downregulation of DCC expression in ventral tegmental area (VTA) dopamine neurons by recruiting the *Dcc* microRNA repressor, miR-218. In turn, this amphetamine regimen leads to disruption of mesocortical dopamine connectivity and deficits in cognitive processing in adulthood, including reduced behavioral control. Whether, exposure to low doses of amphetamine, comparable to those used in therapeutic settings, disrupts miR-218/DCC signaling and mesocortical dopamine development, needs to be established. In this study, we treated male early adolescent C57BL/6 mice (from PND 22 ± 1 to PND 31 ± 1) with saline or with low doses of amphetamine (0.5 mg/kg i.p.) every other day, for a total of 5 injections. One week after the last injection, we measured levels of miR-218, *Dcc* mRNA, and DCC protein in the VTA. We then allowed a separate group of mice to reach adulthood (PND 75 ± 15), to assess behavioral control using the Go/No-Go task. Finally, we performed stereological analysis to estimate the span of the innervation of dopamine axons in the prefrontal cortex and the number/density of their presynaptic sites. We found that: (1) in contrast to the high-dose regimen, low doses of amphetamine in adolescence do not alter *Dcc* mRNA or miR-218 expression in the VTA, but *upregulate* DCC protein levels in this region, one week later; (2) there are no discernable differences in prefrontal cortex dopamine input volume or in the number/density of mesocortical dopamine presynaptic sites between adult mice treated with the saline or low amphetamine dose regimen in early adolescence; (3) strikingly, adolescent exposure to the low dose amphetamine regimen does not lead to impaired behavioral inhibition in adulthood. Instead, this drug treatment induces an overall increase in the rate of correct responses in the Go/No Go task, in comparison to saline-treated groups. These results show that low doses of amphetamine in adolescence lead to different, even opposite dopamine and behavioral effects in adulthood, compared to high doses. These differences may result from the opposite regulation that these doses exert on miR-218/DCC signaling in the VTA.

Disclosures: J. Restrepo: None. **S. Cuesta:** None. **L.M. Reynolds:** None. **C. Popescu:** None. **S. He:** None. **C. Fortin:** None. **J. Epelbaum:** None. **S. Silvestrin:** None. **C. Flores:** None.

Poster

645. Adolescent Development: Mechanisms of Vulnerability

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 645.14/E26

Topic: A.09. Adolescent Development

Title: Locus coeruleus glutamatergic synapses experience divergent forms of plasticity during the adolescence to adulthood transition

Authors: *A. LOCARNO[1], I. MISEVICIUTE[1], F. PAPALEO[2], G. MARSICANO[3], B. LUTZ[4], F. E. GEORGES[5], R. TONINI[1]
[1]Neuromodulation of Cortical and Subcortical Circuits Lab., [2]Genet. of Cognition Lab., Fondazione Inst. Italiano Di Tecnologia, Genova, Italy; [3]Neurocentre Magendie, INSERM U1215, Bordeaux, France; [4]Univ. Med. Ctr. Mainz, Mainz, Germany; [5]IMN-UMR-CNRS-5293, Bordeaux, France

Abstract: The adolescent and adult brains respond differently to psychological stressors, which are encoded at the level of the prefrontal cortex (PFC) and amygdala (Amyg) circuits. This raises the possibility that unbalanced activity between PFC- and Amyg output pathways may contribute to the higher emotional reactivity and stress-related behavior observed during adolescence. The PFC and Amyg send excitatory afferents to the Locus Coeruleus (LC) nucleus, the major source of norepinephrine for the entire forebrain. This neuromodulatory nucleus has been associated with attention, arousal, emotional learning, and stress response. Whether glutamatergic inputs to LC neurons undergo experience-dependent synaptic plasticity and whether this plasticity differs between adulthood and adolescence remains to be established. To address these questions, we investigated spike-timing dependent plasticity (STDP) at excitatory LC synapses. In adult mice (P45-P60), glutamatergic inputs to LC neurons express a Hebbian form of timing-dependent LTD (t-LTD) that relies on CB1 receptor activation, and which is lost in response to social stress. In young mice (P23-P28), we found inverted STDP rules. Furthermore, plasticity in young animals requires the release of Corticotropin Releasing Factor, likely by Amyg projections to the LC. By showing post-natal functional remodeling of LC glutamatergic synapses, our results identify synaptic substrates for some of the different adrenergic-mediated behavioral responses between adolescent and adult subjects.

Disclosures: A. Locarno: None. **I. Miseviciute:** None. **F. Papaleo:** None. **G. Marsicano:** None. **B. Lutz:** None. **F.E. Georges:** None. **R. Tonini:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.01/E27

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH R01 MH105094
NIH T32 MH65215

Title: Sex determines the behavioral and biochemical impact of dopaminergic dysfunction in the DAT Val559 mouse model

Authors: *A. STEWART[1], R. GOWISHANKAR[1,4,5], R. PEART[2], K. SPIESS[1], G. L. DAVIS[1,4], M. K. HAHN[1,3], R. D. BLAKELY[1,3]
[1]Biomed. Sci., [2]Wilkes Honors Col., [3]Brain Inst., Florida Atlantic Univ., Jupiter, FL; [4]Neurosci. Grad. Program, [5]Intl. Scholars Program, Vanderbilt Univ., Nashville, TN

Abstract: Dopaminergic dysfunction has been implicated in multiple neuropsychiatric disorders with a demonstrated sex bias including Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD) and Bipolar Disorder (BPD). The dopamine (DA) transporter (DAT, *SLC6A3*) mutation Val559 exhibits spontaneous DA efflux (ADE) and has been identified in patients with ADHD, ASD, and BPD suggesting that ADE may be a shared etiological factor driving neuropsychiatric disease risk. We now show that sex influences the phenotypic manifestation of tonically elevated extracellular DA in mice. Male DAT Val559 animals display blunted amphetamine- (AMPH) and methylphenidate (MPH)-induced hyperactivity and completely lack a locomotor response to cocaine (COC). In contrast, while COC-induced locomotion was also absent in female DAT Val559 animals, the response of DAT Val559 females to AMPH and MPH was indistinguishable from that of WT mice. When the rewarding properties of COC were assayed, both male and female DAT Val559 mice acquired cocaine conditioned place preference (CPP), with females exhibiting overall higher preference scores. However, male DAT Val559 animals displayed delayed extinction as compared to their WT littermates whereas COC CPP extinction was accelerated in DAT Val559 females. The observed behavioral resilience of female DAT Val559 mice to alterations in psychostimulant responses may stem from a differential impact of the mutation on DAT function. For example, in synaptosomes isolated from the striatum of male mice, we observed a significant rightward shift in potency for AMPH, but not COC, whereas shifts in the potency of DA uptake inhibition were not observed in DAT Val559 females. Further, *in vivo* chronoamperometry revealed an attenuation in dorsal striatal DA clearance in male DAT Val559 mice whereas a similar impact of the mutation was not seen in females. Together these data provide evidence for a sex-dependence to the penetrance of molecular, physiological and behavioral effects of the DAT Val559 variant, underscore the importance of *in vivo* models interrogating the functional impact of DAT mutations, and indicate that the DAT Val559 mouse model offers opportunities to delve into the influence of sex on molecules, neurons, circuits and behaviors that link DA to neuropsychiatric disorders.

Disclosures: A. Stewart: None. **R. Gowishankar:** None. **R. Peart:** None. **K. Spiess:** None. **G.L. Davis:** None. **M.K. Hahn:** None. **R.D. Blakely:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.02/E28

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH RO1 MH105094

Title: Investigating cognitive flexibility in DAT Val559 mice, a construct valid model of DA-associated neuropsychiatric disorders

Authors: *M. J. RABIL[1], G. L. DAVIS[1,3], A. STEWART[1], M. K. HAHN[1,2], R. D. BLAKELY[1,2]
[1]Biomed. Sci., [2]Brain Inst., Florida Atlantic Univ., Jupiter, FL; [3]Neurosci. Grad. Program, Vanderbilt Univ., Nashville, TN

Abstract: Aberrations in dopaminergic neurotransmission have been linked to multiple neuropsychiatric disorders. Given the possibility that this overlapping mechanism is rooted in shared genetic insult(s), the Blakely lab conducted a genetic screen for patients harboring rare, functional coding variation in the dopamine (DA) transporter (DAT) gene, identifying the Ala559Val substitution in two male siblings with Attention-Deficit Hyperactivity Disorder (ADHD) that has also been identified in subjects with Autism Spectrum Disorder (ASD) and Bipolar Disorder. DAT Val559 exhibits a phenotype of basal DA leak, leading to elevations in extracellular DA in DAT Val559 knock-in mice. Previous work in the lab has demonstrated that these animals exhibit waiting impulsivity, which appears to be driven by a heightened motivational state. In addition, the animals exhibit a habitual checking behavior in operant tasks whereby they will continue to seek reward even following reward devaluation, possibly indicative of compulsive perseveration. Here, we evaluate the impact of the DAT Val559 mutation on reversal learning, using a pairwise discrimination paradigm. Initial findings indicate that the DAT Val559 mutant mice do not differ significantly from wild-type (WT) littermates in task acquisition. Ongoing studies are examining changes in the rate by which WT and DAT Val559 animals reverse their activity to select a previously non-rewarded option. Given the presence of habitual behaviors in other operant behavioral tasks, we predict that the mutant mice would fail to inhibit past learned behaviors once the rewarded stimulus is reversed. As deficits in cognitive flexibility are characteristic of children with both ADHD and ASD, disorders in which the DAT Val559 mutation has been identified, DAT Val559 mice could, then, be used as a model to investigate the circuit-level and neurochemical basis for disease-associated cognitive inflexibility.

Disclosures: M.J. Rabil: None. **G.L. Davis:** None. **A. Stewart:** None. **M.K. Hahn:** None. **R.D. Blakely:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.03/E29

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Award MH095044

Title: Screening the *C. elegans* million mutation project library to identify regulators of dopamine signaling

Authors: *O. REFAI[1], P. RODRIGUEZ[1], R. D. BLAKELY[1,2]
[1]Florida Atlantic Univ., Jupiter, FL; [2]FAU Brain Inst., Jupiter, FL

Abstract: Dopamine (DA) is a catecholamine neurotransmitter in both vertebrate and invertebrate nervous systems, including the nematode *C. elegans*. DA modulates a wide variety of behaviors including movement, attention, learning and reward. In humans, disruption of DA levels and signaling is associated with multiple brain disorders such as Bipolar Disorder, Parkinson's disease, Schizophrenia, Attention Hyperactivity Disorder (ADHD), and addiction. The DA transporter (DAT) regulates the spatial and temporal dynamics of extracellular DA. In *C. elegans*, DA is produced by eight neurons in the hermaphrodite (4 CEP, 2 ADE, 2 PDE). Proteins that support DA biosynthesis, DA vesicular packaging and release and DA reuptake are highly conserved across phylogeny. Indeed, a wild-type form of the human DAT can rescue the knockout phenotype of *C. elegans dat-1* mutants, indicating the functional conservation between human and nematode DAT proteins. Thus, the simple *C. elegans* dopaminergic system presents an ideal model to study DA signaling. Mutation in the DA transporter protein (DAT-1) results in a phenotype that we termed Swimming-induced paralysis (Swip), which we used previously to identify novel *dat-1* alleles and genetic determinants of DA signaling (Hardaway et al 2012; 2015; Bermingham et al, 2017). Here, we extend our screening efforts to the *C. elegans* Million Mutation Project (MMP) Library. The MMP Library represents a bank of mutant strains that possess pre-sequenced mutations, usually missense point mutations. We screened 300 MMP lines and identified 38 strains that exhibited a SWIP phenotype. Lines were tested for their locomotion behavior on plates to identify animals with otherwise normal movement. Mutants were then prioritized based on their paralysis strength, with 50% or greater Swip by 10 minutes selected for further analysis. We used the antipsychotic drug and DOP-3 receptor blocker azaperone to validate DA-dependence of Swip in these lines. In this effort, 10 strains showed significant reversal of SWIP paralysis, similar to that of *dat-1* mutants treated with azaperone. Subsequently, strains were outcrossed to an N2 wild-type background at least four times, while monitoring the Swip phenotype, to remove background mutations. To further validate candidate mutants, we have acquired and tested other alleles to validate gene selection, and are validating azaperone results using crosses to *dop-3* and the DA synthesis enzyme *cat-2*, which we previously showed to suppress the SWIP of *dat-1* mutants. Ongoing efforts, using cell-specific gene rescue strategies, are aimed at determining whether these genes exert their effects within DA neurons or act indirectly.

Disclosures: O. Refai: None. **P. Rodriguez:** None. **R.D. Blakely:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.04/E30

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH RO1 DA042156

Title: Epigenetic effects of amphetamine in dopamine transporter regulation: Insights from *C. elegans*

Authors: *S. M. SOSSI[1], K. R. KUDUMALA[1], G. AMBIGAPATHY[2], L. CARVELLI[1]
[1]Brain Inst. and Harriet Wilkes Honors Col., Florida Atlantic Univ., Jupiter, FL; [2]Dept. of Biomed. Sci., Univ. of North Dakota Sch. of Med. & Hlth. Sci., Grand Forks, ND

Abstract: Amphetamine (AMPH) is a psychostimulant that is addictive in nature. Use and abuse of this drug have serious side effects. Nevertheless, it is also used to alleviate symptoms in Attention Deficit Hyperactivity Disorder (ADHD). One well-known mode of action of AMPH is to compete with dopamine (DA) to bind to the dopamine transporter and affect reuptake of extracellular DA as well as by stimulating efflux of intracellular DA. Long-term exposure to this drug may contribute to long-lasting epigenetic changes leading to alterations in gene expression. However, the exact mechanisms that mediate these effects at the genomic level are poorly understood. The nematode *C. elegans* has 8 dopaminergic neurons and the genes involved in the dopaminergic signaling pathway are conserved between the worms and humans. With its amenable molecular, cellular, and genetic tools as well as its short life cycle, *C. elegans* is advantageous for studying heritable alterations caused by drug exposure across multiple generations. Exposure to AMPH results in a behavioral phenotype termed Swimming Induced Paralysis (SWIP) in young adult worms, which has been previously determined to be largely mediated by the dopamine transporter, DAT-1. Here, we took advantage of SWIP phenotype to test the long-term effects of AMPH exposure across generations. We found that adult (F0) worms that were exposed to AMPH during development had a higher AMPH-induced SWIP compared to control-treated animals. Moreover, the F1 and F2 progeny originating from AMPH treated parental worms also showed an elevated SWIP response. Thus, our results show that chronic AMPH exposure during development sensitizes adult worms and their progeny to AMPH, suggesting that AMPH causes heritable alterations in gene expression. Recent studies indicate a major role of epigenetic mechanisms, such as chromatin modifications, in addiction and hence we investigated the role of histone modifications on DAT-1 gene. Using Chromatin Immunoprecipitation (ChIP) assays, we found that animals exposed to AMPH showed significant alterations of specific histone markers at the promoter region of DAT-1 in both adults and progeny. Taken together, our results indicate a potential role for epigenetics in the

mechanism of action of AMPH and provides insights into the regulation of dopamine transporter in normal and pathological states.

Disclosures: K.R. Kudumala: None. **G. Ambigapathy:** None. **L. Carvelli:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.05/E31

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: DA015169

Title: Investigating the behavioral impact of regulated dopamine transporter endocytosis in *Drosophila melanogaster*

Authors: *R. R. FAGAN[1,2,3], C. G. SWEENEY[1,2,3], P. EMERY[1,3], H. E. MELIKIAN[1,2,3]
[2]Brudnick Neuropsychiatric Res. Inst., [3]Neurobio., [1]Univ. of Massachusetts Med. Sch., Worcester, MA

Abstract: Dopamine (DA) is a critical regulator of movement, sleep, reward, and cognition. The presynaptic dopamine transporter (DAT), clears released DA, and thereby significantly impacts DA signaling and homeostasis. Psychostimulants including methylphenidate (Ritalin), cocaine, and amphetamine (AMPH), are competitive DAT inhibitors and substrates that enhance extracellular DA. Genetic DAT ablation in mice and invertebrates results in behavioral defects including hyperactivity, reduced sleep, and altered psychostimulant responses. Multiple DAT coding variants identified in attention-deficit/hyperactivity disorder (ADHD), infantile parkinsonism-dystonia, and autism spectrum disorder probands, support that DAT plays a vital role in maintaining DA homeostasis. DAT surface expression is not static under basal conditions; DAT constitutively recycles to and from the plasma membrane, and protein kinase C (PKC) activation significantly stimulates DAT internalization, which decreases DAT surface levels and function. We previously reported that the neuronal GTPase, Rin (RIT2), binds directly to DAT and is required for PKC-stimulated DAT internalization. While considerable progress has been made to define the mechanisms underlying PKC-dependent DAT surface regulation, it is unclear how DAT trafficking impacts DA-dependent behaviors and signaling. Here we leveraged the model organism, *Drosophila melanogaster*, to directly test how DAT trafficking dysregulation impacts DA-dependent locomotion and sleep. To perturb DAT trafficking *in vivo,* we used the GAL4-UAS system in two ways: 1) we manipulated the DAergic expression and function of Ric, the *Drosophila* Rin ortholog, which is required for PKC-mediated *Drosophila* DAT (dDAT) downregulation in cell lines, and 2) we expressed DAT trafficking-mutants, including the ADHD coding variant R615C, on the dDAT null background. Overexpressing constitutively active Ric

in DA neurons significantly decreased total sleep in adult flies. These flies also exhibited increased DA uptake measured in intact *ex vivo* brains, demonstrating that Ric activity in DA neurons correlates with altered DA-dependent behavior. Ongoing experiments will use RNAi to test whether Ric expression in DA neurons is required for locomotion or sleep. Moreover, we will directly test whether DAT trafficking-dysregulated mutants impact DA-dependent behaviors, including locomotion, sleep, and reward, using *Drosophila* strains that express WT or trafficking-dysregulated human DAT constructs on the dDAT null background. Taken together, these studies will illuminate the role that DAT trafficking imposes on DA-dependent behaviors.

Disclosures: R.R. Fagan: None. **C.G. Sweeney:** None. **P. Emery:** None. **H.E. Melikian:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.06/E32

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant DA035224
NIH Grant DA015169

Title: Presynaptic Gq-coupled receptor activation drives D2-dependent, biphasic dopamine transporter surface trafficking

Authors: *P. J. KEARNEY, H. E. MELIKIAN
Neurobio., UMASS Med. Sch., Worcester, MA

Abstract: Dopamine (DA) is a modulatory neurotransmitter critical for behaviors such as movement and reward, as well as cognitive functions including learning and memory. Aberrant DAergic transmission is implicated in multiple neuropsychiatric disorders including ADHD, Parkinson's disease, and addiction. The presynaptic DA transporter (DAT) spatiotemporally controls DA signaling by rapidly clearing released DA. Given that DAergic signaling is highly sensitive to DAT function, understanding the molecular mechanisms that control DAT function and availability is critical for understanding DA neurotransmission and dysfunction in DA-related disorders. DAT constitutively internalizes and recycles to the plasma membrane, and acute protein kinase C (PKC) activation with phorbol esters stimulates rapid DAT internalization and functional down-regulation. Although considerable progress has been made to define the molecular mechanisms governing basal and PKC-regulated DAT trafficking, it is unclear how DAT is regulated in response to endogenous presynaptic receptors that are activated upstream of PKC, such as Gq-coupled receptors, and how the complex signaling stemming from Gq receptor activation integrate to control DAT surface expression and function. In this study, we conditionally expressed the chemogenetic DREADD (Designer Receptors Exclusively Activated

by Designer Drugs), hM3Dq, in mouse DAergic neurons, and tested the impact of presynaptic Gq activation on DAT surface expression in *ex vivo* striatal slices. Gq activation drove biphasic DAT surface trafficking, with a significant increase in DAT surface expression within 5 minutes in both the dorsal and ventral striatum with a return to baseline in dorsal striatum and a net downregulation in ventral striatum by 10 and 30 minutes. Pharmacological DA depletion and D2 receptor (D2R) inhibition studies revealed that Gq-mediated DAT insertion was dependent upon DA release and D2R activation. Furthermore, activating the endogenous Gq-coupled muscarinic receptor 5 (M5) resulted in similar increases in DAT surface expression within 5 minutes in the ventral striatum in *ex vivo* slices. These studies suggest that DAT surface expression is rapidly modulated in response to presynaptic Gq activation and that a combination of presynaptic signaling and autoreceptor activity impacts DAT surface expression through multimodal trafficking mechanisms. Ongoing studies will leverage pharmacological and novel *in vivo* gene silencing approaches to specifically determine the mechanisms required for Gq-mediated biphasic DAT trafficking, and will test whether Gq-stimulated DAT trafficking impacts DA signaling.

Disclosures: P.J. Kearney: None. **H.E. Melikian:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.07/E33

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant DA015169
NIH Grant DA035224

Title: PKC-stimulated dopamine transporter internalization: Interdependent roles of Rin, Ack1 and transporter amino- and carboxy termini

Authors: *H. E. MELIKIAN, C. G. SWEENEY, B. S. ALEJANDRO, L. C. O'CONNOR, R. R. FAGAN
Neurobio., UMASS Med. Sch., Worcester, MA

Abstract: The neurotransmitter dopamine (DA) is critical for movement, motivation, and reward. Synaptic DA availability is spatially and temporally limited by presynaptic DA clearance, mediated by the DA transporter (DAT). DAT coding variants in patients with DA-related neuropsychiatric disorders clearly illustrate that DAT is vital for DA homeostasis and DA-related behaviors. DAT surface stability is highly plastic, and PKC activation stimulates rapid DAT internalization that acutely diminishes DAT surface levels. The neuronal GTPase, Rin, binds to DAT and is required for PKC-stimulated DAT endocytosis. PKC-stimulated DAT

internalization also requires inactivation of the non-receptor tyrosine kinase, Ack1. However, it is unknown whether Rin and Ack1 are functionally linked to promote PKC-stimulated DAT internalization, nor is it known whether PKC regulates a functional Rin/Ack1/DAT complex. We used GTPase mutants and knockdown to test the mechanistic linkage between Rin, Ack1 and DAT, and used a chimeric transporter approach to test which DAT domains are required for stimulated DAT endocytosis and DAT/Rin interactions. PKC-mediated Ack1 inactivation requires Rin, placing Rin upstream of Ack1 in the PKC-stimulated DAT regulatory pathway. Ongoing studies will examine how Rin knockdown impacts PKC-stimulated Ack1 inactivation and DAT internalization. Given that the DAT intracellular terminal domains are crucial sites for regulating transporter function, surface stability, and protein-protein interactions, we further hypothesized that the Rin- and Ack1-dependent endocytic mechanisms synergistically require the DAT N- and C-termini. To test this possibility, we used a transporter chimera approach in which DAT intracellular termini were replaced with the cognate serotonin transporter (SERT) domains. We found that the DAT N-terminus, but not the C-terminus, is required for PKC-mediated internalization, but not internalization in response to Ack1 inactivation. In contrast, both DAT N- and C-termini are required for stimulated DAT internalization in response to Ack1 inactivation. Preliminary pulldown studies using an extracellular bungarotoxin binding site in DAT suggest that PKC activation decreases the wild-type DAT/Rin association, and that PKC-stimulated DAT/Rin dissociation may require the DAT N-terminus. Taken together, these studies will further elucidate the interplay between two known signaling pathways that control DAT surface expression, and test whether the intracellular termini synergistically coordinate for DAT internalization in response to these signaling events.

Disclosures: H.E. Melikian: None. **C.G. Sweeney:** None. **B.S. Alejandro:** None. **L.C. O'Connor:** None. **R.R. Fagan:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.08/E34

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant DP1DA042078
NIH Grant T32DA007135

Title: Potential role of brain H3Q5 histaminylation in circadian rhythmicity

Authors: *R. M. BASTLE[1], T. RAHMAN[1], A. LEPACK[1], S. FULTON[1], A. AL-KACHAK[1], L. FARRELLY[1], Y. LYU[1], S. ZHAO[3], A. RAMAKRISHNAN[1], N. BHANU[4], R. THOMPSON[5], H. MOLINA[6], H. LI[3], L. SHEN[1], B. GARCIA[4], T. MUIR[5], I. MAZE[1,2]
[1]Dept. of Neurosci., [2]Pharmacol. Sci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Basic

Med. Sci., Tsinghua Univ., Beijing, China; [4]Biochem. and Biophysics, Univ. of Pennsylvania, Philadelphia, PA; [5]Chem., Princeton Univ., Princeton, NJ; [6]Proteomics Resource Ctr., Rockefeller Univ., New York, NY

Abstract: Monoamines are often regarded as neurotransmitters that are released from vesicles at axon terminals. However, recent work has demonstrated that intracellular, non-vesicular monoamines can be covalently added to glutamine (Q) residues on proteins (i.e., post-translationally) via tissue transglutaminase 2 (TGM2) and affect a variety of biological processes. We have previously demonstrated that histone H3Q5 is a potent substrate for monoaminylation and we have uncovered roles for brain H3Q5 serotonylation and dopaminylation in depression- and drug-related behavior. However, H3Q5 histaminylation remains to be explored. Given that brain histamine levels are largely rhythmic across circadian cycles, we sought to explore the role of H3Q5 histaminylation in regulating circadian behavior. We used specific antibodies to detect H3Q5 histaminylation (i.e., H3Q5his) at several time points across 24 h in mouse tuberomammillary nucleus (TMN), the source of brain histamine, using Western blot. We then reduced levels of H3Q5his in the mouse TMN using a lentivirus that mutates the Q5 into an alanine (i.e., LV-H3Q5A) and tested circadian and anxiety-related behavior. Across the 24-h zeitgeber, TMN H3Q5his expression exhibited a rhythmic pattern, where levels appear to rise and fall during the transitions into active (i.e., night) and inactive (i.e., day) periods, respectively. Upon H3Q5his knockdown in the mouse TMN, circadian locomotor was altered compared to controls and the LV-H3Q5A group also exhibited reduced anxiety-like behavior. H3Q5 histaminylation appears to be regulated differentially across circadian periods and itself regulate circadian and anxiety-like behavior in mice. In order to investigate the mechanism for these effects, we performed isothermal titration calorimetry (ITC) to examine binding efficiencies of known epigenetic regulator proteins onto H3Q5his. Interestingly, we found that WDR5 (a WD40-repeat protein involved in depositing methyl groups onto H3K4) tolerates binding to H3Q5 serotonylation, but has significantly reduced binding (~5 fold) onto H3Q5his. Future studies will utilize ChIP-seq for H3Q5his, WDR5, and H3K4me3 in order to identify enriched loci across 24 h in the TMN, coupled with transcriptional profiling using RNA-seq. These experiments may reveal a novel mechanism of how H3Q5 histaminylation influences circadian gene expression and behavior.

Disclosures: R.M. Bastle: None. **T. Rahman:** None. **A. Lepack:** None. **S. Fulton:** None. **A. Al-Kachak:** None. **L. Farrelly:** None. **Y. Lyu:** None. **S. Zhao:** None. **A. Ramakrishnan:** None. **N. Bhanu:** None. **R. Thompson:** None. **H. Molina:** None. **H. Li:** None. **L. Shen:** None. **B. Garcia:** None. **T. Muir:** None. **I. Maze:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.09/E35

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Aberrant chromatin regulatory mechanisms in Down syndrome

Authors: *Y. LU[1], A. LEPACK[1], A. L. EAGLE[5], R. M. BASTLE[2], W. WENDERSKI[7], T. FANUTZA[3], L. FARRELLY[8], A. K. FRIEDMAN[9], J. STAFFORD[10], A. BHATTACHARYYA[11], S. L. FULTON[12], A. AL-KACHAK[1], H. MOLINA[13], H. LI[14], P. J. KENNY[15], R. ROPER[16], R. D. BLITZER[4], A. ROBISON[6], K. BRENNAND[3], I. S. MAZE[2]
[1]Neurosci., [2]Dept. of Neurosci., [4]Dept. of Pharmacol. & Systems Therapeut., [3]Icahn Sch. of Med. at Mount Sinai, New York, NY; [5]Dept. of Physiol., [6]Neurosci., Michigan State Univ., East Lansing, MI; [7]Developmental Biol., Howard Hughes Med. Inst. - Stanford Univers, Stanford, CA; [8]Neurosci., Dept. of Neurosci., New York, NY; [9]Hunter College, City Univ. of New York, New York, NY; [10]NYU LMC, New York, NY; [11]Waisman Ctr., Univ. of Wisconsin Madison Waisman Ctr., Madison, WI; [12]Neurosci., Mount Sinai Icahn Sch. of Med., New York, NY; [13]Rockefeller Univ., New York, NY; [14]Tsinghua Univ., Beijing, China; [15]Dept. of Pharmacol. and Systems Therapeut., ICAHN Sch. of Med. at Mount Sinai, New York, NY; [16]Biol., Indiana Univ. Purdue Univ. at Indianapolis Dept. of Biol., Indianapolis, IN

Abstract: Down syndrome (DS) is the most common genetic cause of intellectual disability worldwide resulting from triplication of chromosome 21 (HSA21) in humans. Despite much progress in understanding the genetics of DS, the genes encoded on HSA21 that directly contribute to intellectual disability, as well as their associated molecular mechanisms, remain incompletely understood. BRWD1 is an uncharacterized, brain enriched chromatin effector protein encoded within the DS critical region 2 on HSA21. BRWD1 is believed to act as a transcriptional activator via its proposed interactions with the SWI/SNF chromatin remodeling complex; however, its roles in the contexts of neurodevelopment and in DS have yet to be studied. Consistent with previous gene expression analyses in human DS brain, we observe that Brwd1 expression is significantly elevated in Ts65Dn mice–a well established model of DS–as well as in neurons derived from hiPSCs from DS subjects. Select histone posttranslational modifications (PTMs), some of which we have already shown to directly interact with BRWD1, are also altered in their expression. We recently demonstrated that genetic re-normalization of Brwd1 expression in Ts65Dn mice significantly rescues deficits in trisomy associated transcription, hippocampal LTP and cognition. Furthermore, exogenous Brwd1 overexpression–via viral-mediated transduction of adult dorsal hippocampal neurons in wildtype animals–also leads to deficits in both contextual and spatial memory. It is therefore our working hypothesis that BRWD1 trisomy in DS brain results in aberrant interactions between BRWD1 and the epigenetic landscape, thereby contributing to transcriptional dysplasticity and cognitive deficits. We are now testing this hypothesis in the following ways: 2) Investigating the mechanistic impact of Brwd1 triplication on gene expression in DS-like brain. We are performing unbiased, epigenome-wide analyses of Brwd1 enrichment–along with associated histone PTMs–in Ts65Dn (+/- rescue) brain, followed by overlay comparisons with gene expression profiles obtained using RNA-seq; and 2) Exploring the impact of Brwd1 triplication on recruitment and activity of specific SWI/SNF chromatin remodeling complexes in Ts65Dn mouse brain using biochemical and genome-wide assessments. These experiments will allow us to mechanistically dissect the

functional consequences of abnormal patterns of chromatin regulation in DS brain and will aid in our understanding of the neuroepigenetic processes associated with brain plasticity.

Disclosures: Y. Lu: None. **A. Lepack:** None. **A.L. Eagle:** None. **R.M. Bastle:** None. **W. Wenderski:** None. **T. Fanutza:** None. **L. Farrelly:** None. **A.K. Friedman:** None. **J. Stafford:** None. **A. Bhattacharyya:** None. **S.L. Fulton:** None. **A. Al-Kachak:** None. **H. Molina:** None. **H. Li:** None. **P.J. Kenny:** None. **R. Roper:** None. **R.D. Blitzer:** None. **A. Robison:** None. **K. Brennand:** None. **I.S. Maze:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.10/E36

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIDA F31 DA045428

Title: Functions for histone dopaminylation in cocaine-induced transcriptional and behavioral plasticity

Authors: *A. LEPACK[1], C. T. WERNER[3], L. FARRELLY[4], A. W. SMITH[5], S. L. FULTON[7], A. F. STEWART[8], R. M. BASTLE[6], Y. LU[1], R. THOMPSON[9], E. S. CALIPARI[10], T. MUIR[9], D. M. DIETZ[11], P. J. KENNY[12], I. S. MAZE[2]
[1]Neurosci., [2]Dept. of Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]Dept. of Pharm and Tox; Res. Inst. on Addictions; Program in Neurosci., State Univ. of New York at Buffalo, Buffalo, NY; [4]Neurosci., Dept. of Neurosci., New York, NY; [5]Pharmacol., [6]Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [7]Neurosci., Mount Sinai Icahn Sch. of Med., New York, NY; [8]Pharmacol. and Toxicology, Univ. At Buffalo, Buffalo, NY; [9]Dept. of Chem., Princeton Univ., Princeton, NJ; [10]Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN; [11]Dept. of Pharm and Tox; Res. Inst. on Addictions; Program in Neurosci., State Univ. of New York At Buffalo, Buffalo, NY; [12]Neurosci., Ichan Sch. of Med., New York, NY

Abstract: Drug abuse is characterized by loss of control over drug intake, as well as persistent drug-seeking behaviors, despite negative consequences to both the drug abuser and those directly affected by their behavior. Given that drug addicts continue to crave and pursue drugs of abuse following extended periods of abstinence and/or treatment indicates that there must be life-long changes that occur in brain to promote these behavioral phenotypes. Persistent changes in neuronal gene expression are known to promote physiological alterations implicated in drug addiction. More recently, cell-type and brain region specific epigenetic mechanisms have also been demonstrated to regulate transcriptional programs contributing to addiction-like behaviors; however, our understanding of how these mechanisms mediate life-long addiction remains

limited. Dopaminergic neurotransmission in the central nervous system plays a critical role in psychostimulant-induced neural plasticity, with alterations in dopamine (DA) production/function being implicated in both the development and treatment of substance abuse disorders. Although packaging of DA by the vesicular monoamine transporter is essential for numerous aspects of reward, recent data have demonstrated the additional presence of 'reserve' pools of extravesicular monoamines in the nucleus of monoamine producing neurons. Our lab has shown that DA can form covalent bonds with histone proteins catalyzed by the tissue Transglutaminase 2 enzyme, specifically on histone 3 glutamine 5 (H3Q5dop). We have demonstrated that chronic withdrawal from extended access to cocaine in rodents, results in high levels of DA accumulation in the nucleus of neurons in the VTA, as well as a robust increase in H3Q5dop. Furthermore, we have shown that inhibition of H3Q5dop in VTA represses DA release following cocaine SA and subsequently represses cocaine-seeking behaviors. Interestingly, we have also observed increased amounts of nuclear DA, as well as accumulation of H3Q5dop, in NAc neurons, a non-DAergic producing projection region of VTA, in extended access cocaine animals following a short (24 hr) withdrawal period. Additionally, blocking H3Q5dop in NAc similarly results in decreased cocaine-seeking behaviors following prolonged withdrawal suggesting a circuit-based phenomenon for H3Q5dop in regulating addictive and relapse associated phenotypes. Taken together, these potentially paradigm-shifting studies promise to aid in our understanding as to how monoamines, specifically DA, function in brain to regulate neurotransmission-independent neuronal plasticity and cocaine-mediated behaviors.

Disclosures: A. Lepack: None. **C.T. Werner:** None. **L. Farrelly:** None. **A.W. Smith:** None. **S.L. Fulton:** None. **A.F. Stewart:** None. **R.M. Bastle:** None. **Y. Lu:** None. **R. Thompson:** None. **E.S. Calipari:** None. **T. Muir:** None. **D.M. Dietz:** None. **P.J. Kenny:** None. **I.S. Maze:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.11/E37

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: MQ15FIP100011
NIDA DP1DA042078
NARSAD

Title: Histone serotonylation and its dynamic effects on DNA methylation

Authors: *L. FARRELLY[1], S. ZHAO[2], R. THOMPSON[3], Y. LU[1], L. SHEN[1], A. RAMAKRISHNAN[1], T. MUIR[3], H. LI[2], I. MAZE[1]

[1]Neurosci., Dept. of Neurosci., New York, NY; [2]Tsinghua Univ., Beijing, China; [3]Princeton Univ., New Jersey, NJ

Abstract: Dynamic changes in histone modifications often precede *de novo* DNA methylation and can affect the overall rate of DNA methyltransferase (DNMT) activities. Moreover, aberrant alterations in these epigenetic processes have been demonstrated to result in various disease states. recently identified a novel chromatin modification in eukaryotic organisms, histone serotonylation, which mediates permissive gene expression in mammalian adult and embryonic brain, as well as in models of serotonergic neuronal differentiation. Furthermore, we have defined its biophysical activities as a putative co-regulator of general transcription factor complex (specifically TFIID) recruitment to H3K4me3 marked chromatin.
Our recent data have provided further evidence that histone serotonylation may have consequential effects on DNA methylation *in vivo* that is reflected by differential DNMT3A activity in the presence of serotonylated histones. Stemming from our observation that histone serotonylation is increased in its enrichment in gene bodies of highly permissive loci, this novel modification may act to recruit DNMT3A to accessible chromatin, thereby potentiating its activity and antagonizing the recruitment of repressive complexes, such as PRC2. Recruitment of DNMT3A may link gene body DNA methylation with differentiation-induced alternative splicing, as H3Q5serotonyl is also involved in the recruitment of various subunits of the Splicesome to regions of permissive chromatin.
These mechanisms may be of critical importance, as histone serotonylation likely directs the activities of DNMTs that may be necessary for maintaining chromatin states of genes implicated in normal neurodevelopment, and perhaps even in adulthood neural plasticity. A multitude of DNA methylation assessments, both in culture and in brain, using genome-wide platforms, such as bisulfite sequencing, will assess the interplay between histone serotonylation and DNA methylation, both in developmental and disease models. The importance of assessing specific genomic locations displaying altered DNA methylation in the presence of histone serotonylation will greatly advance our knowledge of this novel histone modification, as well as provide insights into its aberrant regulation in neurological disease states.

Disclosures: L. Farrelly: None. **S. Zhao:** None. **R. Thompson:** None. **Y. Lu:** None. **L. Shen:** None. **A. Ramakrishnan:** None. **T. Muir:** None. **H. Li:** None. **I. Maze:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.12/E38

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: MQ15FIP100011, MQ: Transforming Mental Health Research Fellowship (PI - Maze)

NIH Grant DP1 DA042078

Title: Histone serotonylation in the adult brain: Novel mechanisms of neuroepigenetic plasticity and disease

Authors: *A. AL-KACHAK[1], L. A. FARRELLY[1], S. L. FULTON[1], A. E. LEPACK[1], R. M. BASTLE[1], Y. LU[1], C. MENARD[1], O. BERTON[2], A. AGUSTINUS[3], S. J. RUSSO[1], Y. DAVID[3], I. S. MAZE[1]
[1]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]NIDA Div. of Neurosci. and Behavior & BRAIN initiative, NIH, Rockville, MD; [3]Chem. Biol. Program, Mem. Sloan Kettering Cancer Ctr., New York, NY

Abstract: The field of neuroepigenetics has grown rapidly over the past few decades and has recently implicated chromatin phenomena in the etiology of several psychiatric disorders including major depressive disorder (MDD). While it has been demonstrated that dysregulation of histone posttranslational modifications (PTMs) may be involved in the deleterious transcriptional processes that promote physiological maladaptations in MDD, the field still has only a limited understanding of the underlying mechanisms contributing to this disorder. While it is clear that serotonergic signaling in brain, or aberrations thereof, plays a critical role in the pathophysiology and treatment of MDD, new data from our laboratory suggest potential alternative mechanisms of action for monoamines-so-called histone serotonylation-whereby, for example, the presence of serotonin in the nucleus of dorsal raphe (DRN) neurons may directly mediate transcriptional responses related to various forms of serotonergic plasticity, and the subsequent mediation of mood. Our preliminary data indicate that histone serotonylation is significantly altered in both postmortem DRN tissues from MDD subjects and in chronically stressed rodents, phenomena that appear to be reversed by antidepressant treatments. Furthermore, potentiation of such alterations in a rodent model of MDD (e.g., chronic social defeat stress, CSDS) induced various molecular and circuit level adaptations throughout the DRN. Our studies provide a causal link between these molecular changes and the persistence of depressive-like phenotypes.
While a myriad drugs exist that target monoaminergic dysfunction in brain, antidepressant treatments are only effective for ~1/3 of individuals with MDD. Therefore, it is important to establish novel approaches that specifically target histone PTMs in a cell-type specific manner *in vivo* to better understand their direct contributions to disease states for the development of future pharmacological interventions. Thus, we have developed novel intein-based chemical methodologies to synthesize specific histone PTMs to more directly assess a functional role for histone serotonylation in depressive-like behaviors.

Disclosures: L.A. Farrelly: None. **S.L. Fulton:** None. **A.E. Lepack:** None. **R.M. Bastle:** None. **Y. Lu:** None. **C. Menard:** None. **O. Berton:** None. **A. Agustinus:** None. **S.J. Russo:** None. **Y. David:** None. **I.S. Maze:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.13/E39

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: P50MH096890

Title: Epigenetic profiling of chromatin accessibility in MDD identifies glial dysfunction in reward-processing cortex

Authors: *S. L. FULTON[1], J. FULLARD[2], J. BENDL[2], K. GLEASON[3], A. LEPACK[4], C. A. TAMMINGA[6], P. ROUSSOS[2], I. S. MAZE[5]
[1]Neurosci., [2]Genet. and Genomics, Mount Sinai Icahn Sch. of Med., New York, NY; [3]Div. of Translational Neurosci. Res. in Schizophrenia, Univ. of Texas Southwestern, Dallas, TX; [4]Neurosci., [5]Dept. of Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [6]Univ. of Texas Southwestern Med. Ctr. at Dallas, Dallas, TX

Abstract: Throughout neurodevelopment and into adulthood, precisely coordinated spatiotemporal regulation of chromatin accessibility and nucleosome dynamics dictates the complex transcriptional programs required for neuronal maturation and function. Recently, our laboratory described a novel mechanistic role for histone turnover in regulating transcriptional plasticity. We found that the H3.3 histone variant accumulates in neuronal chromatin with age, remaining highly dynamic over time. Critically, H3.3 deposition into nucleosomes is required for activity-dependent gene expression, synaptic connectivity and cognition. We now extend these findings to investigate the role of chromatin accessibility and H3.3 dynamics in the neuropsychiatric disease state of Major Depressive Disorder (MDD).
In the Chronic Social Defeat Stress (CSDS) mouse model of depression, we observed increased H3.3 turnover in the prefrontal cortex (PFC) of susceptible, but not resilient, mice. Furthermore, disrupting H3.3 turnover via miRNA KD of H3.3 in the PFC resulted in a pro-resilient phenotype indicating that higher levels of turnover in this region may reflect an aberrant stress response. Interestingly, in the orbitofrontal cortex (OFC), a key cortical region affected in MDD in human clinical cohorts, we found increased H3.3 turnover to be highly cell-type specific; in FAC-sorted tissues, we identified a significant increase in H3.3 only in non-neuronal cells suggesting that glial dysfunction may be a driving force behind MDD-related transcriptional abnormalities. Thus, to profile genome-wide nucleosomal deposition patterns and chromatin accessibility in cell-type specific manner, we used ATAC-seq (*A*ssay for *T*ransposase-*A*ccessible *C*hromatin coupled to next generation sequencing) on FACS-isolated neurons and glia. We identified many differentially accessible open chromatin regions (OCRs) associated with MDD, but only in the non-neuronal cell population. We then investigated the upstream transcription

factors that may bind to these cis-regulatory OCRs and are thus establishing the OFC chromatin signature in MDD, as well as the downstream targets of these OCRs to discover important molecules and pathways involved in the MDD pathophysiology. The current study will greatly advance understanding of how chromatin structural organization in non-neuronal cells affects nucleosome dynamics and gene expression in the context of MDD, and may also identify novel mediators of depression for future therapeutics development.

Disclosures: S.L. Fulton: None. **J. Fullard:** None. **J. Bendl:** None. **K. Gleason:** None. **A. Lepack:** None. **C.A. Tamminga:** None. **P. Roussos:** None. **I.S. Maze:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.14/E40

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant NS040109

Title: Treatment of drug-resistant seizures with chloride extrusion enhancer CLP257

Authors: *V. I. DZHALA, K. STALEY
Dept. of Neurol., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Neuronal chloride concentration ($[Cl^-]_i$) is an important determinant of post-synaptic $GABA_A$-R mediated signaling and cell volume regulation. Altered Cl^- equilibrium results in cell swelling, accumulation of $[Cl^-]_i$, and GABA depolarizing responses, which foster seizures and anticonvulsant resistance. Cl^- equilibrium is mediated by a Donnan system in which the cation-chloride co-transporters (CCCs) KCC2 (Cl^- exporter) and NKCC1 (Cl^- importer) comprise the requisite cation and Cl^- membrane permeability. Under pathological conditions, this permeability may limit the rate at which Cl^- equilibrium and GABA signaling can be restored. We investigated whether altering CCC activity affects $[Cl^-]_i$ in injured neurons, and the downstream effects on GABAergic inhibition and seizures. We tested the mechanism of action and specificity of the putative KCC2 up-regulator CLP257, and KCC2 inhibitors VU 0240551 and VU 0463271 in the organotypic hippocampal slice *in vitro* model of epileptogenesis. Extracellular field potential recordings and two-photon imaging of the transgenic chloride fluorophore Clomeleon were used to monitor neuronal network activity, $[Cl^-]_i$ and neuronal cell volume. We found that: (i) CLP257 improved $[Cl^-]_i$ homeostasis and reduced seizure activity in a concentration-dependent manner; (ii) the $GABA_A$-R antagonist SR95531 (10 μM) prevented the anticonvulsant action of CLP257 (30 μM), and the NKCC1 and KCC2 blocker bumetanide (10 and 200 μM) reduced the anticonvulsant action of CLP257 and the rate of Cl^- reduction; (iii) the VU KCC2 antagonists reduced the frequency of ictal-like discharges but strongly increased the frequency

and power of interictal epileptiform discharges and corresponding Cl^- transients in a dose-dependent manner; (iv) VU 0240551 (10 μM) pro-convulsant actions and corresponding Cl^- transients were not affected by block of CCCs with bumetanide (10 and 200 μM); (v) sodium channel blocker TTX (1 μM) abolished VU 0240551 (10 μM) induced epileptiform discharges and corresponding Cl^- transients without affecting E_{Cl}. Our results indicate that: 1) the anticonvulsant actions of high dose CLP257 (30 μM) are likely partially mediated by increased KCC2 activity; 2) the pro-epileptic action of VU and corresponding Cl^- transients are not mediated by CCC modulation. Our data validate CLP257 as a promising target of investigation for antiepileptic therapies, and highlight the ongoing need to develop more specific activators and inhibitors of KCC2 co-transport.

Disclosures: V.I. Dzhala: None. **K. Staley:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.15/E41

Topic: B.02. Ligand-Gated Ion Channels

Support: NINDS Grant R01NS40109

Title: Characterization of neuronal chloride microdomains

Authors: *N. RAHMATI, K. NORMOYLE, J. GLYKYS, K. STALEY
Harvard Med. Sch. & Massachusetts Gen. Hos, Boston, MA

Abstract: Abstract. Cytoplasmic chloride plays an essential role in the regulation of the polarity of ligand-gated anion channels. Differences in the intracellular chloride concentration ($[Cl^-]_i$) of neurons lead to oppositely directed chloride flow, GABA signaling, and anticonvulsant effects. Therefore, understanding the mechanisms underlying $[Cl^-]_i$ regulation is critical for unraveling the variability in GABA reversal potential (E_{GABA}) and the effects of anticonvulsants. Electrophysiological estimates of cytoplasmic neuronal chloride concentrations are notable for the variance between neurons and also between different compartments of the same neuron. We have confirmed our previously published studies by demonstrating that cytoplasmic chloride concentration varies both in different brain regions (e.g. in cortical vs. subcortical neurons) and in different neurons from the same region. Utilizing multiphoton microscopy and transgenic chloride-sensitive fluorophores, we now demonstrate differences in chloride concentrations in different subcellular cytoplasmic milieus, including cell bodies, dendrites and different segments of the same dendrites both *in vitro* and *in vivo*.
If $[Cl^-]_i$ differs in these microdomains, and this underlies the variance in electrophysiological estimates of the reversal potential for $GABA_A$ receptor-mediated Cl^- currents (E_{GABA}), then the

local E_{GABA} should be predictable from the fluorophore data. To test this hypothesis, we have embarked on characterizing the Cl^- microdomains using both microscopic analysis of the high-sensitivity Cl^- fluorophore SuperClomeleon, and electrophysiological measures of the local E_{GABA} in organotypic slice cultures and dissociated cultured neurons of murine hippocampus. Our data demonstrate that $[Cl^-]_i$ varies in different segments of dendrites, and that the borders of these microdomains are highly stable over a course of an hour. In addition, we show that there is a highly significant correlation between the dendritic $[Cl^-]_i$ calculated by SuperClomeleon and the local E_{GABA} measured by gramicidin-perforated patch-clamp recordings. These studies will shed light on neuronal chloride homeostasis and the existence of functionally significant neuronal Cl^- microdomains.

Disclosures: N. Rahmati: None. **K. Normoyle:** None. **J. Glykys:** None. **K. Staley:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.16/E42

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Comparing phasic dopamine dynamics in the striatum, nucleus accumbens, amygdala, and medial prefrontal cortex

Authors: *Z. R. HOLLOWAY, T. FREELS, J. COMSTOCK, H. NOLEN, H. J. SABLE, D. B. LESTER
Psychology, Univ. of Memphis, Memphis, TN

Abstract: Midbrain dopaminergic neurons project to and modulate multiple highly-interconnected modules of the basal ganglia, limbic system, and frontal cortex. Dopamine regulates behaviors associated with action-selection in the striatum, reward in the nucleus accumbens (NAc), emotional processing in the amygdala, and executive functioning in the medial prefrontal cortex (mPFC). The multifunctionality of dopamine likely occurs at the individual synapses, with varied amounts of phasic dopamine release acting on different receptor populations. Using in vivo fixed potential amperometry in anesthetized mice and electrical stimulation of the medial forebrain bundle, the current study provides a comprehensive, systematic examination of phasic dopamine dynamics in the 4 predominant neural output regions of the nigrostriatal and mesocortical pathways. Amperometric recordings revealed that the striatum (1.86 uM) and NAc (2.03 uM) have significantly greater stimulation-evoked dopamine release than the the amygdala (0.19 uM) and mPFC (0.05 uM). Heterogeneity was also seen in the dopamine half-lives, i.e. the time dopamine remained in the synapse, of these sites. Again, no differences were found in the dopamine half-lives between the striatum and NAc (0.40 and 0.43 sec, respectively), but the half-life of the amygdala (0.85 sec) was twice as long and that of the

mPFC (2.12 sec) was over 5 times as long as the NAc and striatum. These results suggest that dopaminergic innervation and kinetics varies between these systems. Accordingly, when examining overall dopamine supply via a 3 min continuous stimulation, the striatum (11070 uM) and NAc (8157 uM) had increased dopamine available for release than the amygdala (5097 uM) and mPFC (4004 uM). Recordings were confirmed to be dopamine via injections of dopamine, norepinephrine, or serotonin reuptake blockers. The current findings improve understanding of regional differences in dopamine transmission and can lead to more efficient treatments for disorders related to dopamine dysfunction.

Disclosures: Z.R. Holloway: None. **T. Freels:** None. **J. Comstock:** None. **H. Nolen:** None. **H.J. Sable:** None. **D.B. Lester:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.17/E43

Topic: B.02. Ligand-Gated Ion Channels

Title: The relationship between neuronal extracellular matrix, intracellular cytoskeleton, and mobile chloride

Authors: *K. P. NORMOYLE[1,2], K. J. STALEY[2,1]
[1]Neurology, Div. of Child Neurol., Massachusetts Gen. Hosp., Charlestown, MA;
[2]Massachusetts Gen. Hosp., Boston, MA

Abstract: The cytoplasmic concentration of chloride ($[Cl^-]_i$) is actively managed by neurons. $[Cl^-]_i$ varies both developmentally and spatially along the dendrites of neurons. Because $[Cl_i]$ is maintained by equilibrative transporters, variance in $[Cl^-]_i$ raises the possibility of corresponding variance in extracellular chloride concentration $[Cl^-]_o$. Small changes in transmembrane chloride gradient may profoundly affect the response to GABA-A receptor ($GABA_AR$) activation and thus affect the principle mechanism of many anti-epileptic drugs (AEDs). While the action of cation-chloride cotransporters (CCCs) NKCC1 and KCC2 and their differential expression during early development is surely important, data from multiple laboratories now demonstrate that CCCs do not set E_{GABA}. Rather, $[Cl_i]$ and $[Cl_o]$ are determined by a Donnan system of which the CCCs comprise the membrane permeability. Cytoplasmic perimembranous proteins and extracellular glycoproteins comprise the fixed charges of the Donnan system. We propose that this Donnan system determines $[Cl_i]$ and $[Cl_o]$. Importantly, such a system would also be influenced by osmotic forces because the CCCs cotransport water with cations and chloride. As the neuron integrates signals through multiple pathways to regulate cytoskeletal proteins (e.g. actin and microtubules) and extracellular matrix on multiple distinct time scales (tens of seconds to minutes to days/weeks), the Donnan potential both driving chloride flow across open

$GABA_A$Rs and contributing to CCC activity is adjusted dynamically. Differential rates of intracellular and extracellular remodeling of electrically and/or osmotically active species would result in adjustments to $[Cl^-]_i$ and $[Cl^-]_o$, which we measure directly using the genetically encoded ratiometric reporter Super-Chlomeleon (SClm) and the extracellular fluorescence lifetime imaging (FLIM) reagent SBiQ, respectively. Here we present our work studying the relationship between 'fixed' anionic and osmotically active moieties inside and outside the cell and their relationships with $[Cl^-]_i$ and $[Cl^-]_o$.

Disclosures: K.P. Normoyle: None. **K.J. Staley:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.18/E44

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Autoreceptor inhibition of dopamine release in the nucleus accumbens is altered by D2 antagonism and dopamine transporter inhibition

Authors: N. PAIGE[1], *H. J. SABLE[1], D. B. LESTER[2]
[1]Dept. of Psychology, [2]Psychology Dept., Univ. of Memphis, Memphis, TN

Abstract: The mesolimbic dopamine pathway has an established role in disorders such as addiction, ADHD, and schizophrenia. This pathway consists of dopamine cell bodies in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc), which is classically divided into 2 compartments, core and shell. NAc dopamine transmission is continually being regulated via dopamine autoreceptors (DARs) and dopamine transporters (DATs). D2 dopamine receptors have a well-established role as DARs. D3 receptors have also been suspected to function as DARs, although this is debated in the literature. Less is understood about the interaction of DARs and DATs. The present study aimed to distinguish the regulatory role of D2 and D3 receptors on VTA stimulation-evoked dopamine release in the NAc core and shell using in vivo fixed potential amperometry in anesthetized mice. Stimulation parameters specifically designed to assess DAR functioning were applied during dopamine recordings before and after local infusions of D2 or D3 receptor antagonists. To assess the impact of DAT functioning on DAR-mediated inhibition, DAR tests were also employed before and after a systemic injection of the DAT inhibitor nomifensine (10 mg/kg, i.p.). In both the NAc core and shell, infusing a D2 receptor antagonist significantly decreased DAR functioning compared to vehicle infusions, whereas infusions of the D3 receptor antagonist made no differences in DAR-mediated inhibition relative to vehicle infusions. Furthermore, DAR-mediated inhibition was increased following DAT blockade by nomifensine in both the NAc core and shell. Overall, the results indicate no differences between the NAc core and shell in the measured properties of DAR functioning.

Overall, findings indicate D2 receptors but not D3 receptors function as DARs, and DAR functioning is heightened without functional DATs suggesting a potential compensatory relationship. Determining the specific receptor types that serve as DARs and the interplay between DARs and DATs is crucial for understanding disorders related to dopamine dysfunction, especially given that DARs may serve as a therapeutic target for such disorders.

Disclosures: N. Paige: None. **H.J. Sable:** None. **D.B. Lester:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.19/E45

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: High-fat vs. vegan diet: Effects on nucleus accumbens dopamine release in mice

Authors: *M. K. ESTES, J. BLAND, K. ECTOR, D. B. LESTER
Psychology, Univ. of Memphis, Memphis, TN

Abstract: Natural rewards, such as food, and drugs of abuse, such as psychstimulants, are known to increase mesolimbic dopamine activity; however, less is known about the long-term effects of diet on this reward pathway and its response to psychostimulants. In the present study, 3 diets were compared: a high-fat diet (Western Diet), a low-fat vegan diet (Daniel Fast), and a control diet (standard lab chow). C57BL/6J mice began the diet at 7 weeks old, and open field tests were conducted 4, 8, and 12 weeks post diet initiation. Following the 12-week diet period, *in vivo* fixed potential amperometry was used to measure real-time stimulation-evoked dopamine release in the nucleus accumbens of anesthetized mice before and after a drug challenge of the dopamine reuptake blocker nomifensine (10 mg/kg i.p.). The Western Diet mice weighed significantly more than the other diet groups starting 6 weeks post diet initiation. Open field tests revealed the Western Diet mice had decreased locomotor activity relative to the other diet groups (Western Diet = 622 cm, Daniel Fast = 734 cm, and control = 748 cm; $p = 0.04$ and 0.03, respectively), but only on the 4 week testing day. Western diet mice had reduced baseline (pre-drug) dopamine release compared to the other diet groups (Western Diet = 0.32 uM, Daniel Fast = 0.47 uM, and control = 0.54 uM; $p = 0.05$ and 0.01, respectively) and a reduced dopaminergic response to the nomifensine drug challenge (Western Diet = 220%, Daniel Fast = 261%, and control = 291%; $p = 0.01$ and 0.10, respectively). These results indicate that a high fat diet can reduce mesolimbic dopamine functioning as well as this reward pathway's response to a psychostimulant. These findings may be of importance to individuals suffering from and/or seeking treatment for dopamine-related disorders, such as addiction and ADHD.

Disclosures: M.K. Estes: None. **J. Bland:** None. **K. Ector:** None. **D.B. Lester:** None.

Poster

646. Monoamines II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 646.20/E46

Topic: E.05. Brain-Machine Interface

Title: SUVN-502, a pure 5-HT_6 receptor antagonist potentiates the effects of donepezil or memantine on electrophysiological activity in rat hippocampus

Authors: *R. V. NIROGI, G. BHYRAPUNENI, V. S. BENADE, S. DARIPELLI, T. BANDYALA, P. ACHANTA, S. KESHARI SARAF
Suven Life Sci., Hyderabad, India

Abstract: SUVN-502 is a pure and potent 5-HT_6 antagonist being developed for the symptomatic treatment of Alzheimer's disease. SUVN-502 is orally bioavailable and has excellent brain penetration. SUVN-502 exhibited pro-cognitive properties when tested in various rodent models. When administered alone, SUVN-502 increased acetylcholine levels in brain regions involved in learning and memory, providing the neurochemical basis for the pro-cognitive effects in rodent models. Effect of SUVN-502 in combination of donepezil or memantine was evaluated using electroencephalography (EEG) for the modulation in power density of stimulation induced theta in hippocampus. Effect on the hippocampal theta activity was tested after administration of SUVN-502 (1 mg/kg, i.v.) in combination with donepezil (0.3 mg/kg, i.v.) or memantine (0.3 mg/kg, i.v.). Hippocampal theta activity was elicited by electrical stimulation of Nucleus Pontis Oralis in urethane anesthetized male Wistar rats. SUVN-502 produced significant potentiation in the donepezil or memantine evoked theta power in hippocampus. These results provide the electrophysiological evidence that SUVN-502 in combination donepezil or memantine may be beneficial in the treatment of cognitive deficits associated with Alzheimer's disease.

Disclosures: R.V. Nirogi: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Suven Life Sciences Ltd. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. S. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Daripelli:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **T. Bandyala:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Achanta:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Keshari Saraf:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.01/E47

Topic: B.06. Synaptic Transmission

Support: Brain & Behavior Research Foundation.

Title: Metabolism of ^{13}C-labeled glucose reveals altered neuronal oxidation and glutamate-glutamine cycling in UCP2$^{-/-}$ mice

Authors: *G. M. CHOWDHURY[1], Y. JU[2], T. HORVATH[3], G. SANACORA[4], D. L. ROTHMAN[5], K. L. BEHAR[4], G. HERMES[6]
[1]MRRC & Psychiatry, [2]1Department of Psychiatry and Magnetic Resonance Res. Ctr., [3]Dept. of Comparative Med., [4]Dept. of Psychiatry and Magnetic Resonance Res. Ctr., [5]Diagnos. Radiology, Magnetic Resonance Res. Ctr., [6]Dept. of Psychiatry, Yale Univ. Sch. of Med., New Haven, CT

Abstract: Deficits in mitochondrial energy production represent a common thread in the pathologies of numerous brain disorders including major depressive disorder, schizophrenia and Parkinson's Disease. Mitochondria are therefore emerging as markers for disease progression and targets for therapeutic intervention. The mitochondrial uncoupling protein 2 (UCP2), is a key mitochondrial protein contributing to central regulation of energy metabolism and has been linked to physiological processes underlying neurodegenerative disorders and metabolic syndrome in humans and in animal models. Alterations in brain energy metabolism, including reduced glucose utilization and mitochondrial respiration, are observed with impaired UCP2 expression and in the mouse knockout model UCP2-/-. Here, we apply new experimental tools to broaden the search for the role of mitochondrial UCP2 in disease states. Magnetic Resonance Spectroscopy (MRS) offers one such tool, which has been applied recently in individuals with polymorphisms of UCP2 and UCP2 knockout mice. MRS can be readily adapted to measure metabolic pathway flux by use of ^{13}C-labeled substrates. In this study we measured the flow of ^{13}C label into brain glutamate, glutamine and GABA in 12~14 week old UCP2 het (UCP2-/-, n=12), and non-carrier control (UCP2 +/+, n=12) mice following timed (8 min) intravenous infusions of [1,6-$^{13}C_2$] glucose (neuronal and glial substrate) to determine whether dynamic turnover of the major amino acids linked to brain energy metabolism and neurotransmission (glutamate, GABA and glutamine) is altered in the UCP2 mice. Following euthanasia by focused-beam microwaves, brain tissues (hippocampus, HP and pre-frontal cortex, PFC) were dissected and extracted using ethanol and the brain concentrations and ^{13}C enrichments of amino acids determined using ^{1}H-[^{13}C] MRS at 11.74T. We found that in UCP2-/- mice, ^{13}C labeling of glutamate, GABA, and glutamine was significantly lower in PFC (Glu-C4, *$p<0.01$; GABA-

C2, *$p<0.001$* and Gln-C4, *$p<0.001$*) and HP (Glu-C4, *$p<0.01$;* GABA-C2, *$p<0.01$* and Gln-C4, *$p<0.001$*) compared to wild type mice. These findings indicate that the activities of the tricarboxylic acid cycles in glutamatergic and GABAergic neurons and neuron-astroglial neurotransmitter cycles were reduced, suggesting impaired neuronal energy metabolism and neuron-astrocyte substrate cycling. These physiological changes could underlie pathology associated with UCP2 impairment and may provide targets for novel drug development.

Disclosures: G.M. Chowdhury: None. **Y. Ju:** None. **T. Horvath:** None. **G. Sanacora:** None. **D.L. Rothman:** None. **K.L. Behar:** None. **G. Hermes:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.02/E48

Topic: B.06. Synaptic Transmission

Support: NSERC of Canada 05407-2014
onds de Récherche du Québec -Santé

Title: Ovariectomy reduces the suppression of excitatory synaptic transmission induced by physostigmine in layer II of the entorhinal cortex

Authors: *A. A. BATALLAN BURROWES[1], I. A. IASENZA[2], F. CARTER[3], W. SHAMS[4], C. CHAPMAN[5]
[1]Psychology, Concordia Univ., Montréal, QC, Canada; [2]Concordia Univ., Montreal, QC, Canada; [3]Concordia Univ., Montréal, QC, Canada; [4]Psychology, Concordia Univ., Montreal, QC, Canada; [5]Psychology, Concordia Univ., Concordia University, QC, Canada

Abstract: Estrogens are thought to contribute to cognitive function in part through interactions with basalforebrain cholinergic neurons which project to the hippocampus and adjacent cortical regions includingthe entorhinal cortex. Reduced availability of estrogens is associated with a decline in cognitive function,and it is possible that this may be due in part to a resulting impairment in the function of cholinergicinputs to the hippocampal region. Layer II of the entorhinal cortex, which receives strong cholinergicinnervation, contributes importantly to cognitive and mnemonic functions of the hippocampal region byproviding the hippocampus with its main source of cortical sensory input. Acetylcholine results in asuppression of glutamate release at excitatory synapses in the entorhinal cortex. In the present study, weassessed the effects of loss of estrogens on the function of cholinergic terminals indirectly, by comparingeffects of the cholinesterase inhibitor physostigmine (i.e., eserine) on excitatory synaptic transmission inbrain slices obtained from intact and ovariectomized rats. Physostigmine was used as an agonist becauseits effects depend upon amplifying the impact of the endogenous

release of acetylcholine. Ovariectomy wasconducted at ≈60 days of age, and recordings were obtained at 10 to 12 weeks of age. Horizontal acutebrain slices were obtained and field excitatory postsynaptic potentials (fEPSPs) in layer II of theentorhinal cortex were evoked by stimulation of layer I. After baseline recordings in normal aCSF,physostigmine (10 µM) was applied for 15 min. Physostigmine caused a reduction in the peak amplitudeof fEPSPs that persisted during 30 min washout in normal aCSF. However, the application ofphysostigmine caused a smaller reduction in responses in ovariectomized rats (89.5 ± 3.0% of baseline,n=12) relative to intact control rats (80.0 ±3.1% of baseline, n=8; t 18 =-2.12, p<0.05). Subsequentapplication of the muscarinic receptor blocker atropine (1 µM, 15 min) reversed the suppression offEPSPs to above baseline levels in both groups. The blunting of the suppressive effect of physostigmineon evoked excitatory responses in ovariectomized rats may be a result of reduced function in cholinergicterminals in the entorhinal cortex. This is consistent with the idea that loss of estrogens may lead toreduced cognitive function in part through disruption of cholinergic transmission within the entorhinalcortex.

Disclosures: A.A. Batallan Burrowes: None. **I.A. Iasenza:** None. **F. Carter:** None. **W. Shams:** None. **C. Chapman:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.03/E49

Topic: B.06. Synaptic Transmission

Support: MEXT Grant-in-Aid for Scientific Research

Title: Dietary large neutral amino acids suppress kynurenic acid production in rat brain

Authors: *T. FUKUWATARI, A. KUSUMOTO, A. SEKINE, A. MARUYAMA, M. SANO, N. MORI, K. SHIBATA
Dept. of Nutr., The Univ. of Shiga Prefecture, Hikone, Japan

Abstract: At endogenous brain concentrations, the tryptophan metabolite kynurenic acid (KYNA) is a preferential antagonist of the α7 nicotinic acetylcholine receptor. Animal experiments show that elevated KYNA levels reduce glutamate and dopamine levels, and contribute cognitive dysfunction. Patients with schizophrenia show elevated KYNA levels in the brain and cerebral spinal fluid, suggesting the involvement of KYNA in the pathophysiology of schizophrenia. Kynurenine (KYN), the immediate precursor of KYNA, is transported into astrocytes via large neutral amino acid transporters (LATs). We have reported that high tryptophan diet increased KYNA production and reduced dopamine release in rat brain (*J Neurochem* 2011;118:796), that several LATs substrate amino acids reduce KYN uptake and

KYNA production in rat brain *in vitro* (*SpringerPuls* 2015;4:48), and that inhibition of LATs suppresses KYNA production via inhibition of KYN uptake in rodent brain (*Neurochem Res* 2016;41:2256). In the present study, we investigated the effect of large neutral amino acids diets on KYNA and KYN contents in rat brain. Rats were given 1.5% tryptophan supplemented diet with 3% valine, 3% leucine, 3% isoleucine, 1% methionine, 3% phenylalanine or 5% tyrosine for 7 days. The tryptophan supplemented diet increased brain KYNA and KYN contents, and serum KYN concentration to 2.1-, 2.4- and 1.8-fold, respectively. Additional amino acids except for valine suppressed increase of high tryptophan-induced brain KYNA and KYN contents to 0.5-0.8-fold, and failed to affect serum KYN concentration. These results suggest that intake of large neutral amino acids except for valine competitively inhibit KYN uptake by astrocytes via LATs, and thus suppress the increase of KYNA production in the brain. Dietary manipulation of KYNA formation in astrocytes may provide useful approach for the treatment of glutamate and dopamine related disorders.

Disclosures: T. Fukuwatari: None. **A. Kusumoto:** None. **A. Sekine:** None. **A. Maruyama:** None. **M. Sano:** None. **N. Mori:** None. **K. Shibata:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.04/E50

Topic: B.06. Synaptic Transmission

Title: Ethanol modulates kynurenic acid synthesis - in an *in vitro* study

Authors: *H. BARAN, B. KEPPLINGER
Karl Landsteiner Res. Inst. Mauer, Amstetten-Mauer, Austria

Abstract: Background Ethanol interacts at one of the major sites associated with $GABA_A$ receptors. Ethanol exerts antidepressant properties and anti-dementia action is suggested. The study evaluates the action of various physiological and toxic/lethal doses of ethanol on the activity of enzymes synthesizing kynurenic acid (KYNA) kynurenine aminotransferases I, II and III (KATI, KATII and KATIII) in the rat brain and post mortem human brain, in an *in vitro* study.
Material and Methods Human post mortem samples of frontal cortex from the Boltzmann Institute, Institute of Neurobiology, General Hospital Lainz, Vienna, Austria (N = 5) were obtained. Sprague Dawley rats 3 months old male were used (N = 4). The study was performed according to the ethical regulations of the government of Austria. KATs determination performed according to method (H. Baran and B. Kepplinger, Eur. Neuropsychopharmacol., 2014).
Results Ethanol at concentration between 1.05 – 34.5 mM, respectively 0.062 - 2 ‰ lowered

slightly but significantly the activity of KAT II, KAT I and KAT III (between 10 and 15 % of control; $P<0.05$) in the homogenate of human frontal cortex. Moderate effect of ethanol on KAT II and KAT III activities was seen in rat brain homogenate, too. Higher doses of ethanol (non physiological / lethal) (34.5 - 345 mM) reduced doses dependently and significantly the activity of KAT II and KAT III in the rat brain and in the human brain homogenate (between 15 and 30 % of control, $P<0.05$).
Conclusion The present study for the first time demonstrates the ability of ethanol to lower moderately KYNA formation in rat and human brain homogenates. Modulation of KYNA formation by ethanol is interesting and a notable observation, since moderate lowering of KYNA content would constantly try to increase the dopamine neurotransmission which in fact is already affected by alcohol alone causing dependences event. We suggest that modulatory effect of alcohol on KYNA synthesis might be in part involved in the alcohol's action as an antidepressant and likely as an anti-dementia acting putative ligand. The mechanism of ethanol action on KATs activities needs to be further elaborated. All authors have no conflict of interest. Study supported by Sene*Cura* Austria.

Disclosures: H. Baran: None. **B. Kepplinger:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.05/E51

Topic: B.06. Synaptic Transmission

Support: NIH Grant DA035942, DA040626, DA045507, and DA030396

Title: Nicotinic cholinergic receptors in VTA glutamate neurons modulate excitatory transmission

Authors: *Y. YAN[1], C. PENG[1], M. C. ARVIN[1], X. JIN[1], V. J. KIM[1], M. D. RAMSEY[1], Y. WANG[1], S. BANALA[2], D. L. WOKOSIN[1], J. MCINTOSH[3], L. D. LAVIS[2], R. M. DRENAN[1]
[1]Northwestern Univ., Chicago, IL; [2]Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA; [3]Univ. of Utah, Salt Lake City, UT

Abstract: The ventral tegmental area (VTA) is divided into lateral and medial subnuclei. Lateral VTA is mainly composed of dopaminergic and GABAergic neurons. Lateral VTA dopaminergic transmission contributes to reward, addiction, and other psychiatric disorders. Afferent glutamatergic neurons modulate these effects via presynaptic α7 nicotinic acetylcholine receptors (nAChRs). Although vesicular glutamate transporter 2 (VGLUT2+)-expressing neurons in the medial VTA are involved in optically stimulated reward or aversion in rodents, the expression pattern and function of nAChRs in these cells are poorly understood. In this study, we used

molecular, physiological, CRISPR gene editing, and optogenetic techniques to address these questions. Medial VTA neurons are responsive to acetylcholine released from cholinergic axons triggered by presynaptic photostimulation. Medial VTA VGLUT2+ neurons express mRNA and protein subunits known to comprise heteromeric nAChRs. Electrophysiology, coupled with 2-photon microscopy and laser flash photolysis of photoactivatable nicotine, showed nAChR functional activity in the somatodendritic subcellular compartment of VTA VGLUT2+ neurons. Finally, optogenetic isolation of intrinsic VTA glutamatergic microcircuits along with gene editing techniques demonstrated that nicotine potently modulates excitatory transmission within the VTA via heteromeric nAChRs. These results indicate that VTA glutamate neurons are modulated by cholinergic mechanisms and participate in the cascade of physiological responses to nicotine exposure.

Disclosures: **Y. Yan:** A. Employment/Salary (full or part-time):; Northwestern University. **C. Peng:** A. Employment/Salary (full or part-time):; Northwestern University. **M.C. Arvin:** None. **X. Jin:** A. Employment/Salary (full or part-time):; Northwestern University. **V.J. Kim:** A. Employment/Salary (full or part-time):; Northwestern University. **M.D. Ramsey:** A. Employment/Salary (full or part-time):; Northwestern University. **Y. Wang:** None. **S. Banala:** None. **D.L. Wokosin:** None. **J. McIntosh:** None. **L.D. Lavis:** None. **R.M. Drenan:** A. Employment/Salary (full or part-time):; Northwestern University.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.06/F1

Topic: B.06. Synaptic Transmission

Support: NIH SPARC 3OT2OD023859

Title: Nicotinic acetylcholine receptors mediate and modulate cholinergic circuit activity in mouse myenteric ganglia

Authors: J. F. MARGIOTTA, A. KALINOSKI, A. PERRIN, *M. J. HOWARD
Dept Neurosciences, UT Hlth. Sci., Toledo, OH

Abstract: Cholinergic nicotinic acetylcholine receptors (nAChRs) mediate a significant component of transmission in myenteric ganglia, making them critical components of enteric circuitry producing rhythmic, reciprocal activation of intestinal longitudinal and circular muscles. To probe cholinergic myenteric circuits *in-situ*, colon strips from mice engineered to express GCaMP6f in cholinergic neurons were challenged with nAChR specific agonists and antagonists. The resulting changes in GCaMP6f mediated Ca^{2+} fluorescence ($\Delta F/F$) were captured by rapid cell imaging and used to assess agonist sensitivity as well as spontaneous and

induced circuit activity. The pan-specific nAChR agonist DMPP reliably induced increases in both neuronal ΔF/F and in the frequency of ΔF/F fluctuations; both were inhibited by the pan-specific nAChR antagonist D-tubocurarine. nAChRs composed of α7-subunits (α7-nAChRs) are known to mediate and modulate transmission at some autonomic neuron synapses, and RNAseq findings reveal expression of α7-subunit transcripts in myenteric ganglia. Indicative of α7-nAChR participation in myenteric circuits, application of an α7-nAChR selective agonist (GTS-21) increased both ΔF/F levels and fluctuations. Confocal analysis of colon strips treated with Alexa Fluor 488-conjugated α-bungarotoxin (an α7-nAChR-specific neurotoxin) reveals specific labeling on myenteric neuron somas and processes. These findings are consistent with a major role for nAChRs in mediating and modulating transmission at myenteric synapses. They further indicate that functional α7-nAChRs are present in myenteric ganglia and may regulate transmission at some myenteric neuron synapses.

Disclosures: J.F. Margiotta: None. **A. Kalinoski:** None. **A. Perrin:** None. **M.J. Howard:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.07/F2

Topic: B.06. Synaptic Transmission

Support: 16H05507

Title: Cholinergic interneurons facilitate disinhibition of pyramidal neurons in the rat cerebral cortex

Authors: *K. KANEKO[1], S. MATSUMURA[2], Y. OI[3], M. KOBAYASHI[4]
[1]Dept. of Anesthesiolosy, [2]Dept. of Pediatric Dent., Nihon Univ. Sch. of Dent., Tokyo, Japan; [3]Dept. of Anesthesiol., Nihon Univ. Sch. of Dentisitry, Tokyo, Japan; [4]Dept. of pharmacology, Nihon Univ. Sch. Dent., Chiyoda-Ku, Japan

Abstract: The cerebral cortex involves cholinergic interneurons in addition to cholinergic projections from the basal forebrain (BF). Cortical cholinergic interneurons (CCN) are immunopositive for vasoactive intestinal peptide (VIP), and are distributed principally in layers II/III with a bipolar somatic morphology. Several studies have reported that CCN do not exert direct inhibitory postsynaptic response in neighboring pyramidal neurons (Pyr), but indirectly increase spontaneous EPSCs in adjacent Pyr. It is also reported that cortical VIP-immunopositive interneurons are activated by cholinergic inputs from BF, and project to the somatostatin (SST)-immunopositive interneurons and parvalbumin (PV)-immunopositive interneurons, both of which inhibit Pyr. Therefore, it is likely that cholinergic inputs from BF disinhibit excitatory

neurons by exerting VIP-immunopositive interneurons-induced suppression of SST/PV-immunopositive interneurons. However, little information is available in terms of the cellular mechanisms of neuromodulation by CCN. Here, we performed whole-cell patch-clamp recording from CCN (ChAT-tdTomato- and VGAT-Venus-positive) and adjacent GABAergic interneurons and Pyr in the rat insular cortex (IC). CCN rarely projected to Pyr but principally project to low threshold spike (LTSN) or fast-spiking GABAergic neurons (FSN), which frequently induced unitary IPSCs in Pyr. In addition, CCN often mutually connected to other CCN via chemical and electrical synapses, and their repetitive spike firings were often synchronized. GABAergic projections from CCN to LTSN/FSN were attenuated by application of atropine. These results suggest that CCN disinhibit Pyr via GABAergic interneurons. Indeed, simultaneous recording from CCN, other GABAergic interneurons, and Pyr under current clamp condition demonstrated that bath application of acetylcholine induced repetitive spike firing in CCN and this spike firing was followed by enhancement of spontaneous IPSCs in the GABAergic interneurons and reduction of spontaneous IPSCs in Pyr. These effects were mimicked by nicotine. Thus, it is likely that CCN disinhibit Pyr via nicotinic and muscarinic receptors.

Disclosures: K. Kaneko: None. **S. Matsumura:** None. **Y. Oi:** None. **M. Kobayashi:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.08/F3

Topic: B.06. Synaptic Transmission

Support: Smoking Research Foundation of Japan
JSPS KAKENHI grants

Title: A novel aspect of cholinergic transmission in central nervous system

Authors: *I. MURAMATSU, T. MASUOKA, M. NISHIO, T. ISHIBASHI
Dept. of Pharmacology, Sch. of Med., Kanazawa Med. Univ., Uchinada, Ishikawa, Japan

Abstract: In the central nervous system, acetylcholine (ACh) is an important neurotransmitter related to higher brain functions and some neurodegenerative diseases. It is released from cholinergic nerve terminals and acts on presynaptic and postsynaptic ACh receptors (AChRs). Following release, ACh is rapidly hydrolyzed and the resultant choline is recycled as a substrate for new ACh synthesis. However, this classical concept of cholinergic transmission is currently being reevaluated due to new evidence. Quantum release of ACh from striatum cholinergic neurons is reduced by an increase in stimulus frequency, showing an inverse correlation between release probability and neuronal excitability. ACh release is negatively regulated by presynaptic M2/M3- but not M4-muscarinic receptor subtypes. ACh esterase inhibitors including anti-

Alzheimer's disease drugs have bidirectional influences on synaptic ACh concentrations: an increase by inhibition of ACh hydrolysis and a decrease following activation of presynaptic autoreceptors. Synaptic concentrations of ACh are also regulated by uptake of ACh itself. Therefore, ACh acts on surface and intracellular M1-muscarinic AChRs, both of which are independently involved in cholinergic facilitation of long-term potentiation (LTP) in the hippocampus. Choline for ACh synthesis in cholinergic nerve terminals may be mainly supplied from choline at relevant concentration levels present in the extracellular space, rather than recycled from ACh-derived choline. Our study reveals complex mechanisms of ACh release from cholinergic terminals and initiates a new stage in cholinergic transmission and therapeutic strategies for Alzheimer's disease.

Disclosures: I. Muramatsu: None. **T. Masuoka:** None. **M. Nishio:** None. **T. Ishibashi:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.09/F4

Topic: B.06. Synaptic Transmission

Title: Cell-type specific cholinergic modulation of the claustrum

Authors: *A. NAIR[1,2], M. GRAF[2], G. J. AUGUSTINE[2]
[1]Fac. of Sci., Natl. Univ. of Singapore, Singapore, Singapore; [2]Lee Kong Chian Sch. of Med., Nanyang Technological Univ., Singapore, Singapore

Abstract: Neuromodulatory input from acetylcholine (ACh) is known to drive selective attention (Neuron 97: 769). We characterized cholinergic modulation of neurons in the claustrum, a poorly understood brain region hypothesized to be involved in directing attention (TINS 38: 486). Whole-cell patch clamp recordings were used to measure neuronal responses to photostimulation of cholinergic inputs in brain slices prepared from a ChAT-ChR2 transgenic mouse line. We found that all types of claustrum neurons, classified based on their intrinsic electrophysiological properties, exhibited polysynaptic responses to cholinergic input. However, these responses differed according to neuron type: while projection neurons were both excited and inhibited by cholinergic input, interneurons were only excited. Although polysynaptic responses were found in 86% of claustrum neurons, a remarkably small fraction of these neurons (11%) exhibited monosynaptic responses to cholinergic input (measured in the presence of glutamate and GABA receptor blockers). This monosynaptic input was exclusively excitatory and was present in only 3 of the 6 subtypes of claustrum neurons, namely amplitude-adapting and strongly frequency-adapting projection neurons as well as VIP interneurons. This excitatory input was blocked by mecamylamine and, thus, is mediated by nicotinic ACh receptors. Our results show that the claustrum receives excitatory cholinergic input in a cell-type specific

manner and that local circuits further transform the nature of this input. Rapid nicotinic input to the claustrum may improve the signal-to-noise ratio between different cortical inputs received by the claustrum, thereby enhancing processing of task-relevant input and contributing to selective attention.

Disclosures: A. Nair: None. **M. Graf:** None. **G.J. Augustine:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.10/F5

Topic: B.06. Synaptic Transmission

Support: NIH/NIA K01 grant to HL
NIH/COBRE grant to M. Harrington

Title: Decreased synaptic physiological properties in aged central cholinergic neurons

Authors: *S. GRIGORYEV, Y. BESSONOVA, H. LAWAL
Dept. of Biol. Sci., DSU, Dover, DE

Abstract: Decline in acetylcholinergic (ACh) neurotransmission is a key characteristic of aging across different animal species. And this decline is correlated with deficits in cholinergic linked behaviors such as locomotion and learning. However, the precise contribution of cholinergic signaling remains poorly understood. We are interested in determining the contribution of the cholinergic release process to aging through the study of the vesicular acetylcholine transporter (VAChT). VAChT mediates the transport of ACh into synaptic vesicles is essential for synaptic transmission in ACh neurons. Here, our goal is to use the *Drosophila* model to determine how aging alters the synaptic physiology of Projection Neurons (PNs) in the brain. PNs are the principal neurons of the antennal lobe, and they are almost all cholinergic. They release acetylcholine from both their axonal arbors in higher brain regions and from their dendrites in the antennal lobe. These neurons receive direct excitatory synaptic inputs from olfactory receptor neurons (ORNs) which in turn receive odor stimuli from the external environment. Each type of ORN projects to a discrete glomerulus in the antennal lobe and defines an identifiable type of postsynaptic PN. Using whole cell patch clamp recordings, we characterized electrophysiological properties, including action potential generation and neuronal excitability, in the PNs in young and old flies.. We report that some but not all WT PNs fire action potentials at baseline, and that injection of varying levels of current causes a corresponding increase in AP generation. Moreover, our preliminary data show that neuron firing and neuronal excitability are markedly reduced in the old flies. These findings demonstrate that key synaptic physiological properties of

cholinergic projection neurons are altered during aging; and could provide a platform for efforts to develop interventions against the decline observed in neuronal function as organisms age.

Disclosures: S. Grigoryev: None. **Y. Bessonova:** None. **H. Lawal:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.11/F6

Topic: B.06. Synaptic Transmission

Support: NIMH Grant R01MH104638

Title: Differential involvement of distinct types of interneurons in cholinergic-induced oscillations in the basolateral amygdala

Authors: *J. X. BRATSCH-PRINCE, J. W. WARREN, G. C. JONES, A. J. MCDONALD, D. D. MOTT
Dept. of Pharmacology, Physiology, and Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: Acetylcholine (ACh) has been implicated in attention, learning, and memory through its modulatory action in brain areas such as the hippocampus and cortex. One of the proposed mechanisms underlying ACh's actions is the induction of synchronized oscillations that can couple brain regions. In areas of the hippocampus and cortex these oscillations are driven by muscarinic acetylcholine receptor (mAChR)-mediated activation of cholecystokinin (CCK) and somatostatin (SOM)-containing interneurons. The basolateral amygdala (BL) is a brain region important in emotional processing and memory that receives dense cholinergic projections, providing an anatomical basis for cholinergic effects in this region. Despite this dense cholinergic innervation, little is known about cholinergic modulation of BL circuits. This study explores the mechanism of cholinergic-induced rhythmic oscillations in the BL. Using whole-cell recordings, we found that focal puff application of 10mM ACh on BL pyramidal cells (PNs) induced a burst of gamma frequency (30-100 Hz) IPSCs followed by rhythmic theta frequency (4-12 Hz) IPSCs that could entrain synchronized PN firing. Both sets of IPSCs were blocked by bicuculline, but not glutamate receptor antagonists, suggesting direct cholinergic activation of interneurons (INs). The nicotinic antagonist mecamylamine blocked the gamma frequency IPSCs, suggesting they were driven by nicotinic ACh receptors. In contrast, selective blockade of M3, but not M1 mAChRs blocked the theta frequency IPSCs and rhythmic PN firing. Recordings from parvalbumin (PV)-positive, but not SOM-positive INs, revealed ACh-induced currents, suggesting a selective role of PV INs in driving the oscillations. This differs from hippocampal area CA1 and prefrontal cortex where CCK and SOM INs play a prominent role in generating

cholinergic oscillations. Interestingly, while a majority of PV INs showed an M3-sensitive depolarizing response to ACh, some exhibited a hyperpolarizing or biphasic response, suggesting that theta frequency IPSCs are driven by a subset of these PV INs. Collectively, these studies indicate that mAChRs induce theta rhythm in BL through a mechanism different than that in areas of the hippocampus and cortex.

Disclosures: J.X. Bratsch-Prince: None. **J.W. Warren:** None. **G.C. Jones:** None. **A.J. McDonald:** None. **D.D. Mott:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.12/F7

Topic: B.06. Synaptic Transmission

Support: NIMH Grant R01MH104638
NIH-NIGMS Grant T32-GM081740

Title: Input-specific and activity-dependent cholinergic regulation of synaptic transmission in basolateral amygdala

Authors: *S. C. TRYON[1,2], J. W. WARREN[1], M. E. LONG[1], G. C. JONES[1], A. J. MCDONALD[1], D. D. MOTT[1]
[1]Dept. of Pharmacology, Physiol. and Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC; [2]Dept. of Exercise Sci., Univ. of South Carolina, Columbia, SC

Abstract: Cholinergic neurons of the basal forebrain project to cortical and subcortical structures and release acetylcholine (ACh), a neuromodulator critical for attention and learning. Interestingly, cholinergic neurons of the basal forebrain project most densely to the basolateral amygdala (BLa), where ACh is necessary for processing sensory inputs and forming emotional memories. However, the mechanisms underlying this processing are poorly understood. In cortical circuits, ACh facilitates afferent input while suppressing intrinsic transmission, but whether ACh exerts a similar tuning of information processing in the BLa is not known. To investigate this, we used a combination of optogenetics and slice electrophysiology to examine cholinergic modulation of afferent prelimbic (PL), thalamic (THAL), ventral subicular (VS) inputs and intrinsic recurrent projections to BLa pyramidal neurons. We optogenetically released endogenous ACh from the basal forebrain of ChAT-Cre mice, while recording field and whole-cell electrophysiological responses to determine the mechanisms of cholinergic regulation of afferent and intrinsic input to the BLa. Unlike cortex, we found that endogenous ACh significantly inhibited afferent cortical transmission to the BLa, but did not suppress intrinsic transmission. This inhibition of cortical input was blocked by bath application of the muscarinic

antagonist atropine (5 µM), indicating a role for muscarinic acetylcholine receptors (mAChRs) in modulating afferent inputs to the BLa. These results suggest fundamental differences in cholinergic regulation of information processing in cortex and amygdala. To further investigate cholinergic modulation of distinct afferent inputs, experiments using muscarinic agonists and optogenetically released glutamate demonstrated that mAChRs differentially suppress PL, THAL, and VS inputs to the BL, with greatest inhibition of PL and VS inputs and lesser inhibition of THAL inputs. Muscarinic suppression of PL and VS inputs was augmented by the M4 mAChR positive allosteric modulator VU0467154 (3µM), indicating an M4-mediated inhibition of PL and VS pathways. However, when these inputs were stimulated at gamma frequency (40Hz), mAChR-mediated inhibition failed, indicating frequency-dependent filtering by M4 mAChRs. While M4 receptors inhibited THAL input to the BL, there was also a modest inhibition of THAL input by M1 receptors, indicating mechanistic differences in mAChR regulation at this pathway. Together, these findings suggest mAChRs regulate information processing to the BL in an input-specific and activity-dependent manner that is different from that in the cortex.

Disclosures: S.C. Tryon: None. **J.W. Warren:** None. **M.E. Long:** None. **G.C. Jones:** None. **A.J. McDonald:** None. **D.D. Mott:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.13/F8

Topic: B.06. Synaptic Transmission

Support: R01MH104638

Title: Cholinergic modulation of excitability of pyramidal neurons of the basolateral amygdala

Authors: *T. ANDERSON-SIEG, N. VU, J. X. BRATSCH-PRINCE, M. E. LONG, G. C. JONES, J. W. WARREN, A. J. MCDONALD, D. D. MOTT
Pharmacology, Physiology, and Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: Compelling evidence supports a role for cholinergic signaling in attending to and remembering salient experiences, but the precise role of acetylcholine (ACh) in mnemonic processing of these events is not yet fully understood. In the cortex, pyramidal neurons (PNs) are a prominent target of cholinergic input, but are not uniformly regulated by ACh. In this region, ACh acting through M1 muscarinic acetylcholine receptors (mAChRs) can have opposing effects on pyramidal cell excitability in different cortical layers. During a behavioral task, these opposing effects of ACh may be important in confining action potential output to selected neurons, thereby enhancing the signal-to-noise in relevant cortical circuits. Neurons in the

basolateral amygdala (BL) play an essential role in the cellular processes that underlie emotional memory. BL neurons receive very dense cholinergic innervation from basal forebrain, suggesting that acetylcholine plays a central role in regulating BL function. Indeed, pharmacological activation of mAChRs in BL enhances formation and consolidation of fear memories, whereas blockade of these receptors prevents memory consolidation. Despite the importance of mAChRs in emotional learning, the role of these receptors in modulating PNs in distinct BL circuits is poorly understood. In this study we used confocal immunofluorescence, brain slice electrophysiology and tract tracing to investigate cholinergic modulation of excitability of PNs in behaviorally relevant circuits. BL PNs in appetitive and aversive circuits were identified by injection of the retrograde tracer cholera toxin b into nucleus accumbens, ventral hippocampus and infralimbic cortex. We found that nucleus accumbens projecting PNs most densely clustered in the ventrolateral portion of the intermediate BL, while the ventral hippocampal and infralimbic projecting PNs tended to most densely populate the posterior BL. To determine if ACh uniformly depolarizes these projection PNs, whole-cell electrophysiology was used to record responses to ACh. During blockade of glutamate and GABAergic transmission, focal puff application of 10mM ACh onto BL PNs evoked a monophasic depolarizing response in 75% of recorded cells. In contrast, in the remaining cells ACh application evoked a biphasic response, consisting of an initial transient hyperpolarization followed by a prolonged depolarization. These cells did not differ in resting membrane potential or input resistance. Overall, these findings indicate that BL PNs can be segregated based on projection target and suggest differential cholinergic modulation of these cells.

Disclosures: T. Anderson-Sieg: None. **N. Vu:** None. **J.X. Bratsch-Prince:** None. **M.E. Long:** None. **G.C. Jones:** None. **J.W. Warren:** None. **A.J. McDonald:** None. **D.D. Mott:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.14/F9

Topic: B.06. Synaptic Transmission

Support: MH109104

Title: Recruitment of a basal forebrain cholinergic engram in conditioned fear

Authors: *P. M. RAJEBHOSALE[1], D. A. TALMAGE[2], L. W. ROLE[3]
[1]Ctr. for Nervous Syst. Disorders, State Univ. of New York At Stony Brook, Stony Brook, NY; [2]Pharmacol. Sci., [3]Neurobio. & Behavior, Stony Brook Univ., Stony Brook, NY

Abstract: We previously demonstrated that cholinergic signaling in the basolateral amygdala (BLA) is essential for the proper acquisition and retention of fear memories. How the fear

learning process engages basal-forebrain cholinergic neurons (BFCNs) and the circuit mechanisms that might underlie their recruitment are questions that remain unanswered. First, to understand the contribution of BFCNs to fear learning and recall, we asked whether BFCNs are active during fear recall. To do this, we developed viral tools for activity-dependent (AD), Cre dependent (CD), temporally controlled, and permanent labeling of neurons (ADCD). Upon recall of a fear memory, we discovered cholinergic neurons in the nucleus basalis/substantia innominata (nbM/SI) are labeled by ADCD, and that the number of ADCD+ cholinergic neurons was directly related to the animal's behavioral performance. We next asked whether the ADCD+ cholinergic neurons labeled during recall were a result of de-novo activity or if they represented an ensemble recruited and engraphed during the acquisition of the fear memory. To answer this question, we used the ADCD permanent marker to label neurons during fear acquisition and a transient activity marker (cfos-GFP) during fear recall. We observe that nbM/SI cholinergic neurons have higher reactivation in animals who received tone-shock pairings as opposed to either tone alone or homecage controls. We also observe that tone-shock pairing leads to preferential recruitment of the learning-activated cholinergic ensemble during subsequent recall. Based on these observations, we suggest the establishment of a cholinergic engram in conditioned fear. Given these activity patterns of the nbM/SI cholinergic neurons, we investigated the functional consequences of disrupting the cholinergic inputs to the BLA during different phases of fear conditioning. Inhibiting acetylcholine release in the BLA during fear acquisition significantly reduces freezing behavior during tone recall. Additionally, this manipulation alters c-fos induction in the BLA during recall. Inhibiting acetylcholine release in the BLA during fear recall preserved the freezing response to the tone, but dramatically reduced freezing behavior upon termination of the tone. Ongoing studies examine the possible circuit mechanisms engaged by the cholinergic engram including cell type-specific monosynaptic input mapping to BLA excitatory vs. inhibitory neurons and systematic mapping of the density of nbM/SI cholinergic synapses along the anterior-posterior axis of the BLA.

Disclosures: P.M. Rajebhosale: None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.15/F10

Topic: B.06. Synaptic Transmission

Support: Wellcome Trust/DBT India Alliance
DST-India INSPIRE

Title: Yin and yang of cholinergic modulation in the hippocampus

Authors: *R. SHARMA[1], S. NADKARNI[2]
[1]Biol., IISER-PUNE, Pune, India; [2]Indian Inst. of Sci. Educ. and Res. Pune, Pune, India

Abstract: Acetylcholine is a crucial neuromodulator in the hippocampus which can activate both presynaptic as well as postsynaptic signaling cascades and influence a large number of synaptic functions including receptor sensitivity, plasticity and genetic modifications. Pharmacological blocking of cholinergic receptors in the hippocampal formation impairs encoding of new memories and working memories. Acetylcholine, via the differential effects on a family of metabotropic(muscarinic) receptors, can have a paradoxical impact of suppressing synaptic transmission and enhancing the activity of hippocampal neurons over a range of time scales. Expression of acetylcholine receptors, in various parts of the brain, has been classified and molecular cascades that allow diversity of downstream signals have been elucidated in a variety of cells and in-vitro. However, how heterogeneous and concurrent expression of these receptors in the hippocampus modify synaptic transmission and plasticity remains unknown. Both M1 and M4 muscarinic acetylcholine receptors are highly expressed in hippocampal neurons. M1 expression has been reported in soma, dendrites and spines of CA3 and CA1 pyramidal cells. Their activation is seen to cause increased neuronal excitability and enhanced LTP induction. It can also lead to suppression of membrane potassium currents, thereby causing depolarization and suppression of adaptation. M4 is seen to be mainly localized in the presynaptic terminal and is seen to reduce EPSP amplitude at the Schaffer collateral terminals. We develop a multi-compartment model of CA3 and CA1 neurons that include detailed descriptions of the ion channels on the cell membrane. We model activity of M1 and M4 receptors with biophysical realism along with their downstream signaling. This paradigm allows for the investigation of changes in electrical excitability associated with M1 receptors and its effect on calcium signaling for a range of plasticity protocols. It has been suggested that information in the complex graded voltage signals experienced by the soma is not lost in binary form of synaptic transmission (release or no release) at the CA3-CA1 synapse but encoded by presynaptic short term plasticity. Our results show how differential action of M1 and M4 expression and its modulation of electrical excitability couples to synaptic calcium and neuronal excitability to influence synaptic plasticity and transmission at CA3-CA1 synapses.

Disclosures: R. Sharma: None. **S. Nadkarni:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.16/F11

Topic: B.06. Synaptic Transmission

Support: NS022061

MH109104

Title: Role of cholinergic signaling in fear memory

Authors: *L. JIANG[1], D. A. TALMAGE[2], L. W. ROLE[3]
[1]Dept. of Neurobio. and Behavior, [2]Pharmacol. Sci., [3]Neurobio. & Behavior, Stony Brook Univ., Stony Brook, NY

Abstract: The amygdala is a key structure in encoding of fear learning. The Basolateral Amygdala (BLA) receives a massive cholinergic innervation from the basal forebrain including the nucleus basalis of Meynert/ substantia innominata (NBM/SI). With both optogenetic and chemogenetic techniques, we have shown that altering endogenous ACh release effects animal fear behaviors and induces synaptic plasticity in the BLA. In recent work, we used genetically encoded activity probes to map fear memory related circuits. In the BLA, we find that fear conditioned mice have increased numbers of activated (c-fos+) neurons than home cage sibling controls. c-fos GFP positive BLA neurons had higher baseline synaptic inputs but less synaptic plasticity upon acute nicotine challenge. Using an Activity Dependent and Cre Dependent (ADCD) viral tool that we developed, we also examined behavior dependent changes in activity in cholinergic neurons. Combining the transient c-fos GFP labeling and the permanent ADCD labeling, we tested the role of NBM/SI cholinergic neurons in fear memory. Specific clusters of NBM/SI cholinergic neurons are labeled by both fear conditioning and recall. Fear activated cholinergic NBM/SI neurons display increased firing frequency that drops back to control levels within days. Current studies examine fear memory “engram” in both BLA and NBM/SI and further examine changes in electrophysiology properties with engram enrollment.

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

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.17/F12

Topic: B.06. Synaptic Transmission

Title: Cholinergic modulation of reverberatory activity in cultured neuronal networks

Authors: *X. LI, P. LAU, G.-Q. BI
USTC, Anhui, China

Abstract: Reverberatory activity in neuronal cell assemblies has been theoretically considered as neural process underlying short-term memory. Acetylcholine as a neuromodulator in the brain influences neuronal excitability and synaptic transmission thus changes the state of neuronal networks. We have shown previously that small networks of cultured hippocampal neurons

could elicit rhythmic persistent activity following a single brief stimulus, and thus could be used as an in vitro model system to study network reverberation. We found that acetylcholine reduced occurrence probability of the evoked reverberation while enhanced the duration of spontaneous activities in the same network. This opposite effects of acetylcholine on evoked and spontaneous activities were completely rescued by muscarinic antagonist atropine and scopolamine, but not by nicotinic antagonist mecamylamine, suggesting that cholinergic modulation of network activity in this system were primarily through muscarinic receptor signaling. Further study shows that acetylcholine decreased only excitatory but not inhibitory postsynaptic current, suggesting that its inhibition of evoked reverberation was through acetylcholine suppression of excitatory neurotransmission. Meanwhile acetylcholine increased neuron excitability, probably underlying the enhanced spontaneous network activation. The effects of acetylcholine on excitatory synaptic transmission and neuron excitability also could be rescued by muscarinic antagonist scopolamine. These results provide experimental evidence for cholinergic modulation of reverberation and may give insight into basic regulatory mechanism of short-term memory.

Disclosures: X. Li: None. **P. Lau:** None. **G. Bi:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.18/F13

Topic: B.06. Synaptic Transmission

Support: NRF-2016R1D1A1B01015042

Title: Autaptic cultures of single neurons for studying autonomic synaptic transmission

Authors: *S. KANG[1], C.-K. LEE[4], S. KIM[2], S.-W. JEONG[3]
[1]Dept. of physiology, [3]Dept. of Physiol., [2]Yonsei Univ. Wonju Col. of Med., Wonju, Korea, Republic of; [4]Max PlankIinstitute Exptl. of Medizin, Gottingen, Germany

Abstract: Autaptic synapse (called “autapse”) is a self-synapse that is a functional connection between a neuron and itself, and anatomically identified in a variety of brain regions although its functional significance remains little known. On the other hand, many studies have proved that autaptic cultures of the central neurons are experimentally valuable for studying synaptic transmission. Unlike central synapses, basic mechanisms underlying synaptic transmission and plasticity have been poorly elucidated. In the present study, we generated autaptic cultures of single neurons for studying autonomic synaptic transmission. In this regard, the sympathetic neurons were enzymatically dissociated from the superior cervical ganglia or stellate ganglia of neonatal rats (P0-P2), and plated onto agarose-coated culture dishes with microdots of growth-permissive substrates or glial feeder layers. We tested different culture media containing

different types of serum for optimizing culture conditions. Nerve growth factor and ciliary neurotrophic factor were supplemented to the culture media for a long-term culture and induction of cholinergic phenotype, respectively. The neurite growth and formation of autapse were promoted in the L15 and DMEM/F12 containing rat serum. Electrical measurements were performed under whole-cell ruptured configuration of the patch-clamp recording techniques. To evoke synaptic currents, a single neuronal soma was stimulated by a 2 ms depolarizing step from a holding potential of -60 mV to 0 mV. Hexamethonium-sensitive excitatory postsynaptic currents (EPSCs) were observed from four days in culture, which indicates the formation of cholinergic autapse. Interestingly, however, the EPSCs were not completely abolished in the presence of the hexamethonium, suggesting non-cholinergic neurotransmitter release at the autapses. The EPSCs and the readily releasable pool of vesicles increased time-dependently and reached the maximum size around 12-14 days in culture. The spontaneous miniature EPSCs were observed in the presence of tetrodotoxin. The autaptic cultures also exhibited short-term plasticity as demonstrated with a paired pulse stimulation. Taken together, we successfully generated the autaptic cultures of autonomic neurons which exhibit the previously reported characteristics of cholinergic synaptic transmission.

Disclosures: S. Kang: None. **C. Lee:** None. **S. Kim:** None. **S. Jeong:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.19/F14

Topic: B.06. Synaptic Transmission

Support: NIH Grant R21AG055073
NIH Grant R01MH107507

Title: Acetylcholine release indirectly inhibits Schaffer collateral inputs onto CA1 pyramidal neurons via an increase in inhibitory interneuron excitability and the activation of postsynaptic $GABA_B$ receptors

Authors: P. GOSWAMEE, *R. MCQUISTON
Dept Anat/Neurobiol, Virginia Commonwealth Univ., Richmond, VA

Abstract: Activation of muscarinic acetylcholine (ACh) receptors achieved by bath application of muscarinic receptor agonists has been repeatedly shown to presynaptically inhibit both Schaffer collateral (SC) and perforant path (PP) glutamatergic inputs onto hippocampal CA1 pyramidal neurons. Although ACh release has been shown to contribute to synaptic plasticity at the SC input, fewer studies have examined the direct effect of ACh release on glutamatergic transmission at these synapses. Moreover, indirect effects of cholinergic activation of inhibitory

interneurons on glutamatergic synaptic transmission have not been explored. Therefore, we examined the effect of optogenetically released ACh on both SC and PP inputs in hippocampal CA1 pyramidal neurons of genetically modified mouse brain slices. To optogenetically stimulate the release of ACh, we crossed a choline acetyl transferase (Chat) Cre driver mouse line to a ReaChR Cre-reporter mouse line that resulted in the selective expression of ReaChR in cholinergic neurons of the medial septum and diagonal band of Broca complex. To examine glutamatergic synaptic efficacy, we used paired-pulse electrical stimulated of the SC or PP and measured synaptic responses in CA1 pyramidal neurons using whole cell patch clamp methods. Our results showed that optogenetic activation of ACh release prior to paired pulse electrical stimulation of SC inputs significantly reduced the paired-pulse amplitude (P2/P1) ratio measured from individual CA1 pyramidal neurons (n= 30 cells from 11 animals). The reduction of SC paired-pulse ratio could be blocked by atropine (5 μM), CGP 52432 (2 μM), or the inclusion of GDP-β-S in the intracellular patch clamp solution. These observations suggest that ACh release decreased the SC paired-pulse ratio through a muscarinic receptor driven increase in the excitability of inhibitory interneurons that activate $GABA_B$ receptors on CA1 pyramidal cells. In contrast, ACh release resulted in a suppression of synaptic amplitudes and an increase in the PP paired-pulse ratio that was blocked by atropine (5 μM) but not CGP 52432 (2 μM). The PP data suggests that ACh release directly inhibits PP terminals via muscarinic receptor activation independent of inhibitory interneuron activity (10 cells from 6 animals). Thus, our data indicate that ACh release differentially modulates glutamatergic neurotransmission in SC and PP synapses and provides new insights into the diverse mechanisms by which cholinergic modulation affects hippocampal function.

Disclosures: P. Goswamee: None. **R. McQuiston:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.20/F15

Topic: B.06. Synaptic Transmission

Support: NIH Grant K99 NS102429
Jane Coffin Childs Memorial Fund

Title: GABA cotransmission from cholinergic neurons in the cortex and basal forebrain

Authors: *A. J. GRANGER[1], B. L. SABATINI[2]
[1]Harvard Med. Sch., Boston, MA; [2]Neurobio., Harvard Med. Sch. Dept. of Neurobio., Boston, MA

Abstract: Acetylcholine is a major neuromodulator in the brain, important for maintaining alertness, directing attention, promoting learning, and detecting salient sensory cues. While acetylcholine has a net excitatory effect on downstream neurons, we have recently shown that all cholinergic neurons have the potential to package and release the inhibitory neurotransmitter GABA. The purpose of cholinergic neurons releasing two neurotransmitters with apparently contradictory post-synaptic effects is unknown. To answer this question, we have studied the functional role and developmental time-course of GABA corelease from two different populations of cholinergic neurons: cortically projecting neurons of the basal forebrain, and local cortical cholinergic interneurons. Our hypothesis is that both of these neuron populations differentially release GABA and ACh onto different post-synaptic targets to maintain a net excitatory effect on cortical activity.

Disclosures: A.J. Granger: None. **B.L. Sabatini:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.21/F16

Topic: B.06. Synaptic Transmission

Title: Inhibitory role of peripheral GABA receptors on salivation

Authors: J. LEE[1], *D. R. GIOVANNUCCI[2]
[1]Neurosciences, [2]Univ. of Toledo/College of Med., Toledo, OH

Abstract: Autonomic neural activity closely regulates the production and composition of saliva critical for oral health via sympathetic and parasympathetic input from the superior cervical (SCG) and otic (OG) ganglia, respectively. The discovery of peripheral gamma-aminobutyric acid (GABA) and its receptors in the salivary glands, and the observation that treatment of patients with benzodiazepines can induce severe xerostomia, hints at an unexplored mechanism for peripheral regulation of salivary gland function. In the current study, immunofluorescence, electrophysiology, and live-cell calcium imaging were used to elucidate the GABAergic system in the mouse parotid gland and define its effect on acinar cell regulation. Immunofluorescence analysis of SCG and OG indicated GABA-containing nerve fibers and cell bodies, a subset of which colocalized with retrogradely labeled parotid-projecting neurons injected with Fast Blue (FB) tracer. Whole-cell and gramicidin-perforated patch clamp of FB-labeled neurons revealed depolarizing GABAA receptor-evoked currents that inhibited action potential generation and frequency. In addition, RT-PCR showed the expression of multiple GABA receptors in parotid tissue. However, both live-cell calcium imaging and whole-cell recordings of dispersed acinar cells showed no direct impact of GABA treatment to evoke acinar cell currents or calcium signals. In contrast, calcium imaging of parotid tissue slices demonstrated that GABA reduced

calcium signaling evoked by a depolarizing stimulus that this diminishment was blocked by picrotoxin. Our data suggest GABA has no direct effect on parotid acini but may depress salivation by inhibition of autonomic neural inputs. This may be achieved through decreased neuronal excitability at autonomic ganglia via a shunting effect and presynaptically via reduced neurotransmitter release in the parotid gland.

Disclosures: J. Lee: None. **D.R. Giovannucci:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.22/F17

Topic: B.06. Synaptic Transmission

Support: NIH RO1 MH098534

Title: Reducing inhibition improves E/I balance and hippocampal circuit function in PGC-1α null mice

Authors: *D. BHATTACHARYA, A. F. BARTLEY, Q. LI, L. E. DOBRUNZ
Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Alterations in the excitation/inhibition (E/I) balance are thought to contribute to dysfunction in neuropsychiatric and neurodevelopmental brain disorders such as schizophrenia and autism. E/I imbalance can be caused by dysfunction of GABAergic interneurons, leading to enhanced or reduced GABAergic inhibition. As a result, pharmacological modulation of $GABA_A$ receptors could potentially normalize E/I function. Because E/I imbalances can be frequency dependent due to synaptic short-term plasticity, it is not clear whether the same dose that rescues baseline synaptic function would also normalize the E/I balance at higher frequencies. Our lab has previously shown alterations in E/I ratio and hippocampal circuit function in a mouse model of interneuron transcriptional dysregulation. We use mice with deletion of PGC-1α (peroxisome proliferator activated receptor γ coactivator 1α), a transcriptional co-activator that in hippocampus is localized to GABAergic interneurons. Loss of PGC-1α reduces the expression of the calcium binding protein parvalbumin, which mimics molecular aspects of some complex brain disorders. We have previously shown that there is enhanced inhibition, reduced E/I balance, and impaired CA1 circuit function in PGC-1α null mice. Importantly, the E/I imbalance and circuit dysfunction are frequency-dependent, in that the magnitude of the effects are reduced by paired-pulse stimulation at short intervals. Here we tested the extent to which reducing inhibition can restore the dynamic E/I balance and rescue the deficits in circuit function. We used acute CA1 hippocampal slices from young adult PGC-1α wildtype and null mice, and reduced inhibition by partially blocking $GABA_A$ receptors with a low concentration of bicuculline (BIC).

Surprisingly, we found that low dose BIC rescued the E/I balance during paired-pulse stimulation as well as at baseline. BIC also increased the paired pulse ratio of disynaptic inhibition in PGC-1α null slices, suggesting that it is altering interneuron recruitment. BIC improved CA1 output in slices from PGC-1α null mice to levels comparable to wildtype, as measured by E-S coupling. Our results show that modulation of $GABA_A$ receptors can potentially rescue E/I imbalances even when they are frequency-dependent.

Disclosures: D. Bhattacharya: None. **A.F. Bartley:** None. **Q. Li:** None. **L.E. Dobrunz:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.23/F18

Topic: B.06. Synaptic Transmission

Support: NIH R01NS104071
University of Minnesota's MnDRIVE (Minnesota's Discovery, Research and Innovation Economy) Initiative
McKnight Land-Grant Professorship

Title: Long-range inhibitory nNOS cells: Characterization of an inhibitory neuron population in the mouse hippocampus

Authors: *Z. CHRISTENSON WICK[1], Z. MONTES[1], C. H. LEINTZ[1], C. XAMONTHIENE[1], E. KROOK-MAGNUSON[2]
[2]Neurosci., [1]Univ. of Minnesota, Minneapolis, MN

Abstract: The hippocampus has a diverse collection of inhibitory neurons distinguished by their electrophysiological, morphological, and molecular properties. Previous research has laid a substantial foundation for our understanding of inhibitory neurons in the hippocampus; however, recent advancements in tools to selectively target and manipulate neurons allow continued advances in our understanding of inhibitory neuron diversity. Here we report a population of cells appearing to lack prior characterization, which we refer to as LINCs (long-range inhibitory neuronal nitric oxide synthase expressing cells). Our data suggest that LINCs are unique in that they i) provide powerful inhibition to the hippocampus, targeting both deep and superficial pyramidal cells, ii) are capable of producing both postsynaptic GABAA and GABAB receptor-mediated responses, and iii) have long-range projections to several distinct regions of the brain including the tenia tecta. Together, our data suggest that LINCs are a novel and remarkably powerful inhibitory cell type in the hippocampus that may be capable of orchestrating network-wide activity.

Disclosures: Z. Christenson Wick: None. **Z. Montes:** None. **C.H. Leintz:** None. **C. Xamonthiene:** None. **E. Krook-Magnuson:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.24/F19

Topic: B.06. Synaptic Transmission

Support: NSF K01
NIH RISE 5R25GM122722

Title: Effect of alterations in the vesicular acetylcholine transporter on acetylcholine-linked behaviors in *Drosophila*

Authors: *S. WILLIAMS[1], H. O. LAWAL[2]
[1]Biol. Sci., Delaware State Univ., Wilmington, DE; [2]Biol., Delaware State Univ., Dover, DE

Abstract: The proper functioning of the cholinergic neurotransmission system is critical for essential organismal functions such as movement, and learning and memory. Accordingly, a balance in acetylcholine (ACh) levels is important in the regulation of locomotion and cognitive performance. Although reports have shown that increases or deficits in ACh release results in deficits in behavioral and cognitive functions, however, the mechanism through which this occurs is not well understood. *Drosophila Melanogaster* is a useful model for studying acetylcholine-linked behaviors due to it's ability to perform complex cognitive functions such as locomotion and courtship learning. Here we are using the vesicular acetylcholine transporter (VAChT) which mediates the packaging and transport of ACh for subsequent exocytotic release to manipulate ACh release. Specifically, we are measuring the effect of both reduced and increased levels of VAChT expression on locomotion and learning behaviors. We report that reduced *Vacht* expression causes a deficits in locomotion behavior in at least three locomotion assay paradigms measured. Moreover, we also report preliminary data on our assay for the effect of altered *Vacht* expression on courtship learning and memory. Taken together, these data provide evidence for a role for central cholinergic release in the mediation of key neuronal functions and sets the stage for a more detailed behavioral analysis and would inform functional studies in cholinergic neurons.

Disclosures: S. Williams: None. **H.O. Lawal:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.25/F20

Topic: B.06. Synaptic Transmission

Support: BBT IHU-A-ICM Paris
Fondation pour la Recherche Medicale
Agence Nationale pour la Recherche

Title: Role and function of a5-$GABA_A$Rs in the neocortex: A molecular signature of dendritic synapses from Martinotti cells?

Authors: *J. ZORRILLA DE SAN MARTIN[1], C. DONATO[1], A. AGUIRRE[1], C. CABEZAS[1], A. BARBERIS[2], M.-C. POTIER[1], A. BACCI[1]
[1]Inst. Du Cerveau Et De La Moelle Epinière (ICM), PARIS, France; [2]Plasticity of ihibitory networks Lab, Fondazione Inst. Italiano di Tecnologia, Via Morego 30, Genova Italy, Genoa, Italy

Abstract: The neocortex is the site where all sensory information is integrated to generate complex behavior and sophisticated cognitive functions. This is accomplished through the concerted, synchronous, and rhythmic activity of intertwined cortical networks formed by highly heterogeneous neuronal populations. In particular, locally-projecting, inhibitory GABAergic interneurons encompass a vast number of cell subclasses. Some interneurons are specialized in targeting dendrites, whereas others, known as basket cells, innervate the perisomatic region of cortical principal cells (PNs). Here we studied the α5 subunit of the $GABA_AR$, which is believed to contribute significantly to tonic inhibition. We found that, in L 2/3 PNs of mouse somatosensory cortex, α5 provides a negligible contribution to tonic inhibition. Conversely, we found that α5 is specifically expressed at synapses between the dendrite-targeting interneurons Martinotti cells (MCs) thus indicating that GABAergic transmission through α5-containing $GABA_AR$ subtypes is important for synaptic dendritic inhibition. Moreover, our preliminary results revealed the presence of the α5 subunit onto MC dendrites. Using multiple patch-clamp recordings between MCs and different cortical neuron types, our preliminary results suggest that the expression of α5 is always present at synapses made by MCs, regardless of the postsynaptic target. Altogether, these experiments contribute to better define the role of α5 subunit in somatosensory cortex and help understanding if α5-$GABA_ARs$ can be considered as a molecular signature of dendritic synapses from inhibitory circuits involving MCs.

Disclosures: J. Zorrilla De San Martin: None. **C. Donato:** None. **A. Aguirre:** None. **C. Cabezas:** None. **A. Barberis:** None. **M. Potier:** None. **A. Bacci:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.26/F21

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH intramural award to CJM

Title: GABA and glutamate co-release from hippocampal VGluT3-expressing interneurons

Authors: *K. A. PELKEY, D. CALVIGIONI, C. FANG, G. VARGISH, R. CHITTAJALLU, C. J. MCBAIN
NICHD/LCSN, NIH, Bethesda, MD

Abstract: Cholecystokinin expressing interneurons (CCK-INTs) are positioned to powerfully influence hippocampal information processing by providing strong feedforward and feedback inhibition to principal cells (PCs). However, despite a wealth of information describing intricate synaptic details of CCK-INTs (eg. depolarization induced suppression of inhibition (DSI)/asynchronous release (AR)), their network functions remain enigmatic. This relates to the fact that, beyond common developmental origins and CCK expression, CCK-INTs comprise a heterogeneous cohort with unique postsynaptic target preferences and molecular signatures. Interestingly, one subset of CCK-INTs, vesicular glutamate transporter 3- (VGluT3) expressing perisomatic targeting CCK basket cells (VGluT3$^+$CCKBCs), was recently shown to critically regulate theta oscillations and spatial information coding of place cells. Initial reports of VGluT3 expression within this subpopulation prompted speculation that VGluT3$^+$CCKBCs subserve unique computational roles based on their ability to co-release GABA and glutamate. Indeed, in contrast to Dale's principal of "one neuron, one transmitter" recent studies have described a variety of central neurons that utilize more than one classical neurotransmitter including GABA/glutamate co-releasing neurons in subcortical circuits. However, detailed investigation into the functional properties of a pure VGluT3$^+$ CCK-INT cohort, including glutamate release, is currently lacking. Here we demonstrate GABA/glutamate co-release from hippocampal VGluT3$^+$ interneurons using both paired recording and optogenetic approaches. Under baseline conditions the glutamate component of VGluT3$^+$INT-PC transmission is approximately 1/16th of the GABA mediated conductance and is dominantly mediated by AMPA receptors with minimal NMDA receptor contribution. Glutamate release from VGluT3$^+$CCK-INTs exhibits the same hallmark features as GABA release including cannabinoid sensitivity (DSI) and AR during high frequency firing. Surprisingly, we found that the VGluT3 expressing population of hippocampal INTs extends beyond VGluT3$^+$CCKBCs, also comprising subsets of dendrite targeting INTs including minority populations of somatostatin expressing cells such as subsets of O-LM interneurons. Preliminary optogenetic evaluation also supports functional glutamatergic output

from these dendrite targeting interneurons. Further investigations will aim to uncover physiological, and potential pathological, roles for glutamate release from VGluT3$^+$ INTs in local circuit processing.

Disclosures: K.A. Pelkey: None. **D. Calvigioni:** None. **C. Fang:** None. **G. Vargish:** None. **R. Chittajallu:** None. **C.J. McBain:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.27/F22

Topic: B.06. Synaptic Transmission

Support: BBT program, IHU-A-ICM, Paris, France
Fondation Recherche Medicale, France
Agence Nationale de Recherche, France

Title: Specific alterations of GABAergic sub-circuits in the prefrontal cortex of a mouse model of Down syndrome

Authors: J. ZORRILLA DE SAN MARTIN[1], C. DONATO[1], A. AGUIRRE[1], M.-C. POTIER[1], *A. BACCI[2]
[1]ICM - Inst. du Cerveau et de la Moelle épinière, Paris, France; [2]Inst. du Cerveau et de la Moelle Epiniere (ICM), Paris, France

Abstract: Trisomy (TS) 21 is a human condition produced by the triplication of chromosome 21 and is characterized by mild to severe cognitive deficits. This condition has been successfully modeled in mice; notably, Ts65Dn, the most widely studied model generated so far, reproduces the cognitive deficits observed in humans, and shows marked reduction of synaptic plasticity (LTP) both in vivo and in vitro. Interestingly, it was shown that both features can be recovered by selective block of the α5 subunit of the $GABA_AR$, corroborating the hypothesis of over-inhibition as an underlying mechanism of TS-related cognitive deficits. However GABAergic interneurons are highly diverse and specialized in inhibiting different compartments of principal cortical neurons, and specific alterations of inhibitory sub-circuits in TS mice remain unknown. Here we found that in cortical layer 2/3, α5-$GABA_ARs$ are expressed selectively at synapses between dendrite-targeting, somatostatin-positive Martinotti cells (MCs) and pyramidal neurons (PNs). This was demonstrated in dual whole-cell recordings using X98 mice expressing GFP specifically in MCs, and the use of a specific α5 inverse agonist (α5IA). Interestingly, α5-$GABA_ARs$ had a negligible contribution to tonic inhibition onto layer 2/3 PNs.
This finding prompted the question whether this cortical GABAergic sub-circuit is specifically altered in DS. We first confirmed that α5-$GABA_ARs$ are expressed at MC-PN synapses also in

TS mice. Importantly, however, we found a 2-fold increase at unitary MC-PN GABAergic connections in TS, as compared to WT. This was accompanied by a decrease of paired pulse ratio, suggesting a presynaptic alteration of dendritic inhibition from MCs. Furthermore, glutamatergic recruitment of MCs by PNs was also increased by near 2-fold. We are in the process of determining the mechanisms underlying this enhanced MC-PN-MC circuit loop in TS mice, and test if it is specific for this GABAergic interneuron subclass. Altogether, these results confirm the presence of α5 at MC-PN synapses and show that dendritic inhibition from MCs is specifically affected in TS, indicating this inhibitory loop as a potential therapeutic target for this condition.

Disclosures: J. Zorrilla de San Martin: None. **C. Donato:** None. **A. Aguirre:** None. **M. Potier:** None. **A. Bacci:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.28/F23

Topic: B.06. Synaptic Transmission

Support: 5R01GM058055-18

Title: Optical measurements of anesthetic action on GABA exocytosis

Authors: *I. A. SPEIGEL, H. C. HEMMINGS, Jr
Anesthesiol., Weill Med. Col. of Cornell Univ., New York, NY

Abstract: General anesthetics are powerful psychoactive drugs that produce therapeutic as well as dangerous neurological effects. Although they have been in use for over 170 years, we do not fully understand how these drugs disrupt neural function to cause loss of consciousness, amnesia, and immobility. Volatile anesthetics such as isoflurane disrupt synaptic transmission and inhibit the vesicular release of neurotransmitters, with GABA release from interneurons being significantly less sensitive than glutamate release. The molecular basis for this difference remains unknown. Identifying the responsible presynaptic features would uncover fundamental determinants of anesthetic sensitivity, but a direct comparison of anesthetic actions on glutamatergic versus GABAergic synaptic physiologies and neurotransmitter release mechanisms is limited without a means to selectively measure and manipulate GABAergic exocytosis.
To identify isoflurane's effect on GABAergic synaptic vesicle exocytosis at the level of the individual neuron, we are performing live-cell imaging of GABA release using pHluorin-based optical biosensors expressed in transgenic primary hippocampal neuron cultures, wherein GABAergic interneurons are distinguished by the expression of genetically-encoded fluorescent

markers. We expect that these optical exocytosis measurements will enable interneuron-specific analysis of anesthetic action, and reveal potential variance in isoflurane sensitivity, yielding novel observations of isoflurane's effects on GABAergic signaling. This information is critical to further the understanding of the cellular and behavioral effects of anesthetics, as interneurons modulate nearly every aspect of neuronal excitability and network function, with specialized subpopulations serving distinct roles in circuit function.

Disclosures: I.A. Speigel: None. **H.C. Hemmings:** None.

Poster

647. Synaptic Transmission: Modulation: ACh, Amino Acids, and GABA

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 647.29/F24

Topic: B.06. Synaptic Transmission

Support: ZIAAA000407
Integrative Neuroscience Initiative on Alcoholism

Title: Action of $G_{i/o}$ DREADDson GABAergic projections within the basal ganglia

Authors: *D. M. LOVINGER[1], L. VOYVODIC[2], K. P. ABRAHAO[2]
[1]Chief, Lab. Integrative Neurosci, [2]Lab. Integrative Neurosci, Natl. Inst. on Alcohol Abuse and Alcoholism Rockville Office, Rockville, MD

Abstract: Chemogenetic neuromodulation mediated by the hM4Di designer receptor exclusively activated by designer drug (DREADD) has been shown to involve G protein-coupled inwardly-rectifying potassium (GIRK) channels. However, Gi/o-coupled receptors influence other effectors including voltage-gated calcium channels and adenylate cyclase. In addition, *in situ* hybridization studies indicate that GIRK channels are not expressed in the medium-sized striatal projection neurons (MSNs). Nonetheless hM4Di-mediated chemogenetic modulation of striatal direct and/or indirect pathways alters behaviors. Thus, it is important to assess the cellular mechanisms involved in DREADD alteration of striatal projection pathways. To this end, we examined effects of hM4Di DREADD activation on MSN excitability and synaptic transmission onto neurons within the basal ganglia using transgenic mice, optogenetics and whole-cell patch-clamp recording. Activation of the hM4Di receptors with the otherwise pharmacologically inactive agonist clozapine n-oxide (CNO; 10 µM) inhibited GABAergic opto-evoked inhibitory postsynaptic currents (oIPSCs) in the substantia nigra pars reticulata resulting from activation of striatonigral MSNs. In contrast, CNO did not inhibit oIPSCs at synapses on MSNs made by hM4Di-expressing pallidostriatal projecting (arkypallidal) neurons. These results indicate hM4Di G_i-coupled DREADDs are able to inhibit neurotransmitter release in neuronal populations in a

GIRK channel-independent manner. We are now studying the mechanisms underlying this effect and we also examine the effect of other putative DREADD agonists.

Disclosures: D.M. Lovinger: F. Consulting Fees (e.g., advisory boards); Elsevier journal editor. **L. Voyvodic:** None. **K.P. Abrahao:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.01/F25

Topic: B.06. Synaptic Transmission

Title: A comparison of botulinum toxin A light chain and heavy chain gene fragments in adenoviral vector-mediated gene-based synaptic inhibition

Authors: *L. DI, Y. KIM, M. S. TORA, O. P. KEIFER, Jr., Y. H. CHEN, P. HANNIKAINEN, A. DONSANTE, B. J. MADER, N. M. BOULIS
Dept. of Neurosurg., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Introduction: Botulinum toxin, the standard of care for a variety of peripheral nervous system disorders, suffers from its transient effects and central nervous system toxicity. Vector-mediated gene transfer has the potential for cell-specific, sustained neural inhibition through botulinum toxin gene expression. Here, we tested the adenoviral vector-mediated transfer of select botulinum toxin/A (serotype A) gene fragments in focal neural inhibition without cytotoxicity.
Methods: Adenoviral vectors encoding different botulinum toxin/A domains - light chain, light chain and receptor binding domain, and light chain and translocation domain - were injected into rat spinal cords at 4×10^4 transforming units to test their neural inhibitory effects. To assess for dosage dependency, vectors were also tested at 4×10^5 and 4×10^6 transforming units. Pre-surgical baseline and post-operative motor function was measured by Basso-Beattie-Bresnahan open-field locomotor scoring, grip strength, and rotarod performance. After 3-weeks of postoperative behavioral testing, rats were euthanized, and spinal cords were immunostained and counted for neuronal nuclei to assess cytotoxicity from transgene expression. Prior to injection, vectors were tested *in vitro* in HEK293 cells to control for differences in transduction efficiency.
Results: Animals injected with adenoviral vectors containing genes for the light chain and receptor binding domain displayed the most consistent and sustained deficits in open-field assessment, grip strength, and rotarod performance. Rats injected with adenovirus containing light chain showed spontaneous recovery at 16 days post-injection, coinciding with the cessation of adenoviral gene expression. Spinal cord neuron counts revealed no signs of cytotoxicity between treatment groups and controls at injection titers of 4×10^4 and 4×10^5 but not at 4×10^6 transforming units. *In vitro* testing showed no difference in transduction efficiency between

vectors and there were no differences in neuron density compared to controls.
Conclusion: These results suggest that vector-mediated gene transfer of botulinum toxin light chain and receptor-binding domain is most effective at synaptic inhibition without cytotoxicity. This gene-based approach at focal neuromodulation may hold future applications in the treatment of neurological disease and the study of neural circuitry. Furthermore, these data suggest that the heavy chain may play a role in the characteristic persistence of botulinum neurotoxin/A synaptic inactivation that is yet unexplained.

Disclosures: L. Di: None. **Y. Kim:** None. **M.S. Tora:** None. **O.P. Keifer:** None. **Y.H. Chen:** None. **P. Hannikainen:** None. **A. Donsante:** None. **B.J. Mader:** None. **N.M. Boulis:** F. Consulting Fees (e.g., advisory boards); Agilis, MRI Interventions, Voyager, Oxford Biomedica, Q Therapeutics, Neuralstem Inc, Switch Bio Holdings..

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.02/F26

Topic: B.06. Synaptic Transmission

Support: NIH Grant DA034648
NIH Grant GM007240

Title: Mechanisms of presynaptic suppression of GABA release by opioid receptors in the hippocampus

Authors: *X. J. HE[1], M. R. BANGHART[2]
[1]Biol. Sci., Univ. of California San Diego, LA Jolla, CA; [2]Neurobio., Univ. of California San Diego, La Jolla, CA

Abstract: Opioid receptors are prominent in interneurons of the hippocampus where they modulate GABAergic inhibition onto pyramidal cells. Mu opioid receptor (MOR) activation is known to suppress GABA release from parvalbumin (PV) basket cells in the CA1 region, which positions opioids to affect spike timing, oscillations, and synchronization of neuronal populations in the hippocampus. Although the delta opioid receptor (DOR) is also prominent in the hippocampus, its functional role in distinct interneuron classes has not been established, nor have the molecular mechanisms that underlie MOR and DOR-mediated suppression of synaptic transmission. Using a combination of electrophysiology and optogenetics, we discovered that both MOR and DOR strongly inhibit GABA release from PV+ basket cells in a mutually-occlusive manner. Although both receptors appeared to utilize a presynaptic mechanism, they were differentially prone to desensitization. We further characterized the molecular mechanisms of opioid receptor-mediated suppression using two-photon calcium imaging and pharmacology

and found evidence for modulation of processes downstream of voltage-gated calcium channel activation. Our results suggest a previously unappreciated role for DOR in modulating perisomatic inhibition in the hippocampus and reveal the molecular mechanisms by which both MOR and DOR regulate GABA release from PV basket cells in CA1.

Disclosures: X.J. He: None. **M.R. Banghart:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.03/G1

Topic: B.06. Synaptic Transmission

Support: KAKENHI 26290026
KAKENHI 17H03563

Title: CAPS1 finely regulates the exocytosis of synaptic vesicles in calcium- and/or synapse type-dependent manners, affecting on learning and memory

Authors: *C. ISHII[1], Y. SHINODA[2], T. SADAKATA[3], Y. SANO[1], Y. ISHII[1], N. SHIBANO[1], Y. KATO[1], M. YAMAZAKI[1], A. YAMATO[1], T. FURUICHI[1]
[1]Dept. of Applied Biol. Sci., Tokyo Univ. of Sci., Noda, Japan; [2]Tokyo Univ. of Pharm. and Life Sci., Hachioji, Tokyo, Japan; [3]Gunma Univ., Maebashi, Japan

Abstract: Presynaptic exocytosis of synaptic vesicles (SVs) is a fundamental event in the synaptic transmission. Although various kinds of synaptic molecules have been shown to regulate synaptic exocytosis, a more subtle and fine-tuning mechanism remains unclear as an elaborate cellular device for neural information processing. Recent studies have demonstrated that Calcium-dependent activator protein for secretion 1 (CAPS1) is involved in the exocytosis of SVs as well as that of dense-core vesicles (DCVs). In this study, we analyzed the involvement of CAPS1 in the basic transmission and plasticity of hippocampal synapses. Besides, we evaluated the impact of CAPS1-mediated SV exocytosis on learning and memory in mice. To address these issues, we utilized Emx1-Cre-mediated forebrain-specific CAPS1 conditional knockout (cKO) mice because of the neonatal lethality of CAPS1 conventional knockout mice. Electrophysiological recordings revealed that basal synaptic transmission was severely suppressed at both CA3-CA1 and dentate gyrus (DG)-CA3 synapses which are respectively high and low presynaptic expression of CAPS1 protein. Intriguingly, long term potentiation (LTP) was not impaired at CA3-CA1 synapses but greatly inhibited at DG-CA3 synapses. In addition, SypHy-based live cell imaging using cultured hippocampal neurons acutely deleted CAPS1 gene showed that synaptic release from CAPS1-deleted neurons was significantly suppressed. However, increased $[Ca^{2+}]_i$ rescued SV release in these neurons. These physiological results

suggest that CAPS1 regulates SV exocytosis differently at least two synapses of the hippocampal trisynaptic circuit and in a Ca^{2+}-dependent manner. Consistent with this inference, behavioral tests revealed that CAPS1 cKO mice showed significant impairments in only some but not all of hippocampus-related tasks, indicating that CAPS1-mediated heterogeneous mechanisms between DG-CA3 and CA3-CA1 synapses underlie hippocampus-dependent learning and memory. Taken together, we conclude that CAPS1 is critical to regulating SV exocytosis, specifically to initiate the priming of SV with low $[Ca^{2+}]_i$. Moreover, the contribution of CAPS1 to the synaptic release depends on synapse types of the trisynaptic circuit, presumably because of molecular diversity from synapse to synapse, reflecting the task-dependent memory impairments. Our results suggest CAPS1 is a unique cellular device for information processing in the hippocampus.

Disclosures: C. Ishii: None. **Y. Shinoda:** None. **T. Sadakata:** None. **Y. Sano:** None. **Y. Ishii:** None. **N. Shibano:** None. **Y. Kato:** None. **M. Yamazaki:** None. **A. Yamato:** None. **T. Furuichi:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.04/G2

Topic: B.06. Synaptic Transmission

Support: NIH grant EY10291
NIH grant MH101679
NIH grant DK109204
NIH grant T32 GM07628

Title: Modulation of synaptic transmission: Quantitative analysis of Gbg specificity to a_{2a} adrenergic receptor and SNARE

Authors: *Y. YIM[1], K. BETKE[2], W. MCDONALD[4], R. GILSBACH[5], Y. CHEN[6], K. HYDE[2], Q. WANG[6], L. HEIN[5], H. E. HAMM[3]
[1]Pharmacol., [3]Dept. of Pharmacol., [2]Vanderbilt Univ. Sch. of Med., Nashville, TN; [4]Vanderbilt Univ., Nashville, TN; [5]Univ. of Freiburg, Freiburg, Germany; [6]Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Modulation of neurotransmitter exocytosis by activated $G_{i/o}$ coupled G-protein coupled receptors (GPCRs) is a universal regulatory mechanism used both to avoid overstimulation and to influence circuitry. One of the known modulation mechanisms is Gβγ interaction with soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE). There are 5 Gβ and 12 Gγ subunits, but specific Gβγs activated by a given GPCR and the specificity to effectors *in vivo* are not known. Presynaptic α_{2a}-adrenergic receptors (α_{2a}ARs)

in both adrenergic (auto α_{2a}ARs) and non-adrenergic neurons (hetero α_{2a}ARs) inhibit neurotransmitter release and affect various physiological functions such as anesthetic sparing and working memory enhancement. With a quantitative MRM proteomic analysis of neuronal Gβ and Gγ subunits to detect neuronal Gβ and Gγ subunits, several mouse models including transgenic Flag-α_{2a}ARs, knock-in HA-α_{2a}ARs, and other biochemical techniques such as co-immunoprecipitation, we investigate the specificity of Gβ and Gγ subunits to α_{2a}ARs in both adrenergic (auto α_{2a}ARs) and non-adrenergic neurons (hetero α_{2a}ARs), and SNARE in presence of epinephrine. $G\beta_2$, $G\gamma_2$, $G\gamma_3$, and $G\gamma_4$ preferentially interact with activated auto α_{2a}ARs while $G\beta_4$ and $G\gamma_{12}$ preferentially interact with activated hetero α_{2a}ARs. We also detect a subset of Gβ and Gγ subunits interacting with SNARE upon auto α_{2a}ARs activation. Further understanding of Gβγ specificity on its downstream signaling, especially Gβγ-SNARE interaction, offers new insights into the normal functioning of the brain and lead to identification of potential pathophysiological states in which the Gβγ-SNARE interaction may be dysregulated. These studies yield additional insights into $G_{i/o}$-coupled GPCR-mediated regulation of exocytosis.

Disclosures: Y. Yim: None. **K. Betke:** None. **W. McDonald:** None. **R. Gilsbach:** None. **Y. Chen:** None. **K. Hyde:** None. **Q. Wang:** None. **L. Hein:** None. **H.E. Hamm:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.05/G3

Topic: B.06. Synaptic Transmission

Support: The ministry for Health and Wellfare Affairs Grant HI15C3026

Title: Iqsec3 controls activity-dependent npas4-mediated gabaergic synapse development

Authors: *D. B. PARK[1], S. KIM[1], J. KIM[2], S. HONG[3], S. KIM[1], H. KIM[1], E. YANG[4], J. JEON[3], J. KIM[3], H. KIM[4], E. CHEONG[2], J. KO[1], J. UM[1]
[1]DGIST, Dalseong-gun, Korea, Republic of; [2]Yonsei-University, Seoul, Korea, Republic of; [3]KAIST, Daejeon, Korea, Republic of; [4]Korea Univ. Col. Med., Seoul, Korea, Republic of

Abstract: Organization of mammalian inhibitory synapses is thought to be crucial for normal brain functions, but its molecular mechanisms have been largely undefined. IQSEC3, a guanine nucleotide exchange factor for ADP-ribosylation factor (ARF-GEF), is a GABAergic synapse component that directly interacts with gephyrin. Here, we show that IQSEC3 acts in a synaptic activity-dependent manner to regulate GABAergic synapse development *in vivo*. GABAergic synapse-specific transcription factor Npas4 directly binds to the promoter of *Iqsec3* and regulates its transcription. Moreover, IQSEC3 functions downstream of Npas4 in orchestrating GABAergic synapse development in both dendritic and somatic compartments. Strikingly, a

variety of activity-altering regiments inducing Npas4 upregulation concurrently increased the IQSEC3 expression levels, prominently in somatostatin-positive GABAergic interneurons in hippocampal CA1 stratum oriens, which were compromised in Npas4 knockout (KO) mice. Furthermore, expression of wild-type (WT) IQSEC3, but not the ARF-GEF-inactive mutant (dominant-negative; DN), normalized altered GABAergic synaptic transmission in both dendrites and soma of Npas4-deficient CA1 pyramidal neurons. Collectively, our results demonstrate that IQSEC3 is a key GABAergic synaptic component organized by Npas4 activity- and ARF activity-dependent gene programs to coordinate functional excitation-to-inhibition balance *in vivo*.

Disclosures: D.B. Park: None. **S. Kim:** None. **J. Kim:** None. **S. Hong:** None. **S. Kim:** None. **H. Kim:** None. **E. Yang:** None. **J. Jeon:** None. **J. Kim:** None. **H. Kim:** None. **E. Cheong:** None. **J. Ko:** None. **J. Um:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.06/G4

Topic: B.06. Synaptic Transmission

Support: NIH Grant MH083317
NIH Grant MH109280
NIH Grant NS082007
NIH Grant NS090083
NIH Grant AG051773
NIH Grant AG045781

Title: Adulthood ErbB4 is critical for normal GABA release and behaviors

Authors: *H. WANG[1], F. LIU[2], W. CHEN[3], X. SUN[4], W. CUI[1], Z. DONG[1], K. ZHAO[2], H. ZHANG[1], E. FEI[3], B.-X. PAN[3], B.-M. LI[3], W.-C. XIONG[1], L. MEI[1]
[1]Neurosciences, Case Western Reserve Univ., Cleveland, OH; [2]Neurosciences and Regenerative Med., Augusta Univ., Augusta, GA; [3]Inst. of Life Sci., Nanchang Univ., Jiangxi, China; [4]Dept. of Neurosci., Guangzhou Med. Univ., Guangdong, China

Abstract: Neurotrophic factor Nrg1 and its receptor, ErbB4, play critical roles in neurodevelopment. Meanwhile, studies suggest their expression and regulation in synaptic transmission in adult brain. In agreement with their roles in neurodevelopment, Nrg1 and ErbB4 are susceptibility genes of schizophrenia, which has been treated as a developmental disorder. However, it is not clear whether E/I imbalance at adult stage contributes to the deficits in Nrg1-ErbB4 signaling-deficient mice, which cannot be addressed by routine genetic strategy. In this

study, we generated the iKO and rKO mice to temporally control the deletion or expression of ErbB4. We found adult ErbB4 deletion in iKO mice caused behavioral deficits and GABA release deficiency, recapitulating phenotypes in ErbB4 null mice. In contrast, morphological deficits observed in ErbB4 null mice was not induced after adult ErbB4 deletion. In rKO mice, we found the behavioral deficits caused by ErbB4 loss-of-function during development could be mitigated by restoring ErbB4 expression at adult stage. The mitigation effect might be due to the rescued GABA release probability but not morphological attenuations. These findings suggest that the ErbB4 signaling at adult stage is both necessary and sufficient for maintaining the normal behaviors and synaptic transmission, and targeting to Nrg1-ErbB4 signaling might benefit post-development treatment of relevant schizophrenia.

Disclosures: H. Wang: None. **F. Liu:** None. **W. Chen:** None. **X. Sun:** None. **W. Cui:** None. **Z. Dong:** None. **K. Zhao:** None. **H. Zhang:** None. **E. Fei:** None. **B. Pan:** None. **B. Li:** None. **W. Xiong:** None. **L. Mei:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.07/G5

Topic: B.06. Synaptic Transmission

Support: John R. Evans Leaders Fund grant - Canada Foundation for Innovation
Discovery Grant- Natural Sciences and Engineering Research Council of Canada
Early Career Investigator Pain Research Grant - Canadian Pain Society and Pfizer Canada

Title: Loss of STEP61 couples BDNF-driven loss of inhibition to NMDAR potentiation in rodent and human spinal pain processing

Authors: *C. M. KANDEGEDARA[1,2], A. DEDEK[1,2], J. XU[3], E. C. TSAI[2], P. J. LOMBROSO[4], M. E. HILDEBRAND[1]
[1]Carleton Univ., Ottawa, ON, Canada; [2]Neurosciences, Ottawa Hosp. Res. Inst., Ottawa, ON, Canada; [3]Connecticut Mental Hlth. Ctr., New Haven, CT; [4]Yale Univ. Sch. Med., New Haven, CT

Abstract: Chronic pain is a debilitating condition with few safe and effective treatments. To develop novel therapeutics, we must identify the molecular determinants of pathological pain. However, the majority of pre-clinical pain research relies exclusively on rodent models of pain. Thus, proof-of-concept human tissue studies are urgently needed to bridge the rodent to human translational divide. Runaway excitability within the spinal dorsal horn is a critical mediator of chronic pain. Using the rodent nerve injury model of neuropathic pain, we have previously

shown that BDNF-mediated loss of inhibition (disinhibition) gates the potentiation of excitatory GluN2B NMDAR responses at lamina I dorsal horn synapses (Hildebrand *et al*, 2016, Cell Reports). However, what links these two distinct pathological pathways and whether this mechanism underpins other pathological pain states remain unknown. Here, we show that KCC2-dependent disinhibition is coupled to increased GluN2B-mediated synaptic NMDAR responses in the rodent CFA injection model of inflammatory pain, with an associated downregulation of the phosphatase $STEP_{61}$. We find that decreased activity of $STEP_{61}$ is both necessary and sufficient to prime subsequent phosphorylation and potentiation of GluN2B NMDARs by BDNF at lamina I synapses. Blocking disinhibition reversed the downregulation of $STEP_{61}$ as well as inflammation-mediated behavioural hypersensitivity. Through patch clamp recordings on viable human lamina I neurons, we show for the first time that GluN2B-containing receptors dominate NMDAR responses at human lamina I synapses. We subsequently developed a human *ex vivo* BDNF model of chronic pain using spinal sections from "neurological determination of death" organ donors 1-2 hours following aortic cross clamping. We found that BDNF downregulates KCC2 and $STEP_{61}$ and upregulates phosphorylated GluN2B at human dorsal horn synapses. Our results demonstrate that $STEP_{61}$ is the molecular brake downstream of KCC2-dependent disinhibition that is lost to drive the potentiation of excitatory GluN2B NMDAR responses in rodent and human models of pathological pain. The *ex vivo* human BDNF model may thus form a translational bridge between rodents and humans for identification and validation of novel molecular pain targets.

Disclosures: C.M. Kandegedara: None. **A. Dedek:** None. **J. Xu:** None. **E.C. Tsai:** None. **P.J. Lombroso:** None. **M.E. Hildebrand:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.08/G6

Topic: B.06. Synaptic Transmission

Support: Korean Health Technology R&D Project HI14C2136
Korean Health Technology R&D Project HI14C2137

Title: MAPK-dependent presynaptic potentiation in the LHb is responsible for depressive behaviors

Authors: *H. PARK, H. RYU, S. ZHANG, S. KIM, C. CHUNG
Konkuk Univ., Seoul, Korea, Republic of

Abstract: Emerging evidences suggest that the lateral habenula (LHb), recently proposed to be involved in depressive disorders, is a part of clock system in our brain. Disrupted circadian

patterns are one of commonly observed symptoms in human patients with depression. Recently, we reported that synaptic transmission in the LHb is temporally variable. Here, we showed that temporal variation no longer exists in the LHb of a well-established rodent model of depression. Either exposure to a stressor or incubation with corticosterone abolishes the presynaptic temporal variation of synaptic transmission in the LHb. We also found that altered mitogen-activated protein kinase (MAPK)-dependent signaling upon the activation of glucocorticoid receptors (GRs) mediates the abolishment of temporal variations in the LHb. The selective inhibition of MAPK kinase (MAPKK, MEK) activity in the LHb restores the temporal variations of synaptic transmission of the LHb even after the exposure to stressors. Moreover, the blockade of MAPK signaling before exposure to stress successfully prevents depressive symptoms including behavioral despair and helplessness in the acute learned helpless animal model of depression. Our study delineates the cellular and molecular mechanisms responsible for previously reported abnormal presynaptic enhancement of LHb neurons in animal models of depression, which critically participate in mediating depressive behaviors.

Disclosures: H. Park: None. **H. Ryu:** None. **S. Zhang:** None. **S. Kim:** None. **C. Chung:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.09/G7

Topic: B.06. Synaptic Transmission

Support: NIH grant R15 MH085280-01
Ramapo College Foundation Grant

Title: Sex differences in endocannabinoid-modulation of neurotransmission during adolescence

Authors: A. FERRARO, P. WIG, *C. G. REICH
SSHS/Psychology, Ramapo Col. of New Jersey, Mahwah, NJ

Abstract: Work in our lab demonstrated that hippocampal CB1 receptor (CB1R) levels are lower in female adolescent animals compared to males (Reich et al., 2009). Following 21 day exposure to chronic mild stress, CB1 increased in females while decreasing in males; thus suggesting that hippocampal CB1 responds differentially to stress depending on sex. Several other lines of converging evidence clearly indicate a functional sex difference in the endocannabinoid system and behavioral reactions to exogenous cannabinoids in both humans and animals (Rubino and Paralaro, 2011). However, there remains a paucity of data how these sex differences are manifested physiologically. We, therefore, investigated adolescent sex differences in rat endocannabinoid function. Field excitatory post-synaptic potentials were recorded from CA1 in Sprague-Dawley rat (40-60 days old) hippocampal slices. All drugs were

bath applied after a 10 min baseline with appropriate positive and negative drug controls as necessary. All sample sizes were greater than n=5, the size needed for 80% statistical power. Our studies show that exogenous activation of CB1 (CB1 agonist, WIN 55-212-2) enhances excitatory neurotransmission (fEPSPs) in the CA1 area of female hippocampal slices, while it classically decreases excitatory transmission in males. The latter is due to a CB1-mediated suppression of glutamate release. In females, we now provide evidence that CB1-modulation of excitatory neurotransmission results from enhanced CB1-mediated suppression of GABAergic neurotransmission (inhibitory). Further observations suggest that the following contribute to the mechanism for augmented suppression of inhibition in females: 1) constitutive CB1 activity at GABAergic synapses, 2) enhanced tonic eCB output and 3) Estrogen receptor α. These results clearly demonstrate sex differences in the dendritic layer of CA1 and further extend data on sex differences in the CA1 perisomatic layer.

Disclosures: A. Ferraro: None. **P. Wig:** None. **C.G. Reich:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.10/G8

Topic: B.06. Synaptic Transmission

Title: SUVN-G3031, H3 receptor inverse agonist modulates brain neurotransmitters with role in the treatment of narcolepsy

Authors: *V. BENADE, V. KAMUJU, S. GANDIPUDI, G. BHAYRAPUNENI, P. JAYARAJAN, K. BOJJA, K. KANDUKURI, S. MANCHINEELLA, R. NIROGI
Suven Life Sci. Ltd, Hyderabad, India

Abstract: Numerous studies have demonstrated that brain histamine plays a crucial role in maintenance of wakefulness, attention, learning and other cognitive processes. SUVN-G3031, a potent H3 receptor inverse agonist (hKi of 8.7 nM with more than 100 fold selectivity against the related GPCRs) is being developed for the treatment of narcolepsy and other sleep related disorders. SUVN-G3031 exhibited desired pharmacokinetic properties and brain penetration. First in human, Phase 1 studies are completed under US IND and SUVN-G3031 has shown drug-like properties with desirable pharmacokinetic profile, safety and tolerability in healthy human volunteers. In the current study, SUVN-G3031 was evaluated in brain microdialysis for evaluation of neurotransmitters like acetylcholine, histamine, dopamine and norepinephrine in male Wistar rats. Additional neurochemical studies were carried out to evaluate the in vivo functional nature of the test compound and its effect on the tele- methylhistamine as a possible biomarker for clinical studies. SUVN-G3031 blocked R-α-methylhistamine induced water intake and produced dose dependent increase intele-methylhistamine levels in rat and mice brain and

cerebrospinal fluid. A single oral administration of SUVN-G3031 produced significant increase in acetylcholine, histamine, dopamine and norepinephrine levels in the cortex. SUVN-G3031 produced no change in the dopamine levels of striatum and nucleus accumbens indicating that SUVN-G3031 may not have addiction liabilities. Results from the current studies and electroencephalographic (EEG) studies provide a strong evidence for the potential utility of SUVN-G3031 in treatment of narcolepsy and other sleep related disorders.

Disclosures: V. Benade: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Kamuju:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Gandipudi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **G. Bhayrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Bojja:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Kandukuri:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Manchineella:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.11/G9

Topic: B.06. Synaptic Transmission

Support: Algae Dynamics Inc.
MITACs
NSERC

Title: Cannabidiol regulates mesolimbic dopamine system transmission through peroxisome proliferator-activated receptor gamma signaling in the nucleus accumbens

Authors: *T. D. JUNG, W. J. RUSHLOW, S. R. LAVIOLETTE
Anat. and Cell Biol., Western Univ., London, ON, Canada

Abstract: Cannabis contains two compounds that produce opposite effects. Delta-9-tetrahydrocannabiol (THC), the main psychotropic component of cannabis, has been shown to induce anxiety and schizophrenia-like symptoms. In contrast, cannabidiol (CBD), the non-psychotropic component, demonstrates potential as a promising treatment for both anxiety and schizophrenia. Although the precise mechanisms underlying the effects of THC and CBD are unclear, evidence suggests that the mesolimbic dopamine (DA) system is implicated in their effects. The mesolimbic DA system includes DA projections from the VTA to the NAc. The inhibitory GABA projections from the NAc regulates VTA DA release. The mesolimbic DA

system is carefully regulated through the endocannabinoid system which consists of endocannabinoid type 1 receptors (CB1R). Through CB1R signaling, endogenous cannabinoids modulate the excitatory glutamate and inhibitory γ-aminobutyric acid (GABA) inputs onto VTA DA cells. The phytocannabinoid THC binds to CB1R and disrupts the endocannabinoid system to amplify VTA DA signaling. It is believed that this amplification of VTA DA transmission underlies THC's ability to induce anxiety and schizophrenia-like behaviours. In contrast, CBD produces its therapeutic effects through the attenuation of VTA DA transmission. Unlike THC, CBD has a weak affinity for CB1R and it is unclear which receptors mediate the effects of CBD. One type of receptor that binds CBD is the peroxisome proliferator-acitvated receptor gamma (PPARγ). PPARγ is a nuclear transcription factor that colocalizes with GABA neurons. A past study by de Guglielmo et al. reported that PPARγ activation in the rostromedial tegmental nucleus (RMTg) decreases VTA DA release to the NAc. The RMTg contains a high density of GABA neurons that inhibit VTA DA release and it was found that the attenuation of VTA DA activity by PPARγ activation was mediated through GABA signals from the RMTg. Given that PPARγ is highly expressed in the NAc which also projects GABA neurons to the VTA, we hypothesized the following: PPARγ activation in the NAc will similarly decrease VTA DA release through the augmentation of NAc GABA signaling. Using in-vivo electrophysiology, we report that intra-NAc CBD infusions decreased VTA DA activity. The co-infusion of CBD with a selective PPARγ antagonist blocked the effect of CBD alone. In addition, the combination of a subthreshold dose of CBD with a selective PPARγ agonist synergistically decreased VTA DA signaling. These results demonstrate a novel potential nuclear receptor mechanism through which CBD produces its effects in the mesolimbic DA pathway.

Disclosures: T.D. Jung: None. **W.J. Rushlow:** None. **S.R. Laviolette:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.12/G10

Topic: B.06. Synaptic Transmission

Support: DK092651

Title: Corticosterone rapidly inhibits vagal afferent to NTS signaling via cannabinoid subtype 1 receptors

Authors: F. J. SHAFFER, J. E. M. LINDBERG, I. N. KARATSOREOS, *J. H. PETERS
Dept. of Integrated Physiol. and Neurosci., Washington State Univ., Pullman, WA

Abstract: Centrally, vagal afferent terminals release the excitatory neurotransmitter glutamate (GLU) onto neurons in the nucleus of the solitary tract (NTS) and integrate direct gastrointestinal

signals with ongoing NTS activity and circulating hormones. Glucocorticoid levels increase rapidly in response to stress, fasting, as well as exhibit a diurnal rhythm; all conditions that impact feeding. In this project we investigated the rapid, membrane delimited effects of corticosterone on GLU and GABA signaling in the NTS using patch-clamp electrophysiology on acute brainstem slice preparations containing the NTS and central vagal afferent terminals. Brainstem slices were isolated from adult male C57BL/6 mice and recorded for 3-4 hours following isolation. We found that bath application of CORT rapidly suppressed both presynaptic GLU and GABA release onto NTS neurons. We observed a large decrease in the frequency of spontaneous GLU release as well as an inhibition of action-potential evoked release. While the effect on spontaneous GABA release was rapidly reversed, the inhibition of glutamate was much more prolonged. The effect of CORT was blocked by mifepristone, localized intracellular G-protein inhibition, and phenocopied by dexamethasone; consistent with rapid glucocorticoid receptor (GR) mediated signaling. To elucidate a potential mechanism of these fast effects, we investigated the contribution of the retrograde endocannabinoid (eCB) signaling system, which has been reported to transduce non-genomic GR signals. Pharmacological blockade of the cannabinoid type 1 (CB1) receptor (AM251 or AM4113) blocked CORT induced suppression of GLU release, as did genetic deletion of CB1 receptors. These results demonstrate that fast GLU and GABA signaling can be suppressed in the NTS via GR mediated eCB signaling with distinct time courses. The net impact on NTS signaling will be a function of the balance between GLU and GABA signaling. This provides a plausible mechanism whereby the NTS may integrate circulating endocrine signals with fast neurotransmission to control food intake.

Disclosures: F.J. Shaffer: None. **J.E.M. Lindberg:** None. **I.N. Karatsoreos:** None. **J.H. Peters:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.13/G11

Topic: B.06. Synaptic Transmission

Support: P50 AA010761
T32 AA007474
R37 AA009986

Title: Effects of chronic intermittent ethanol exposure on excitatory inputs onto cerebellar purkinje neurons

Authors: *P. A. ZAMUDIO-BULCOCK[1], J. J. WOODWARD[2]
[2]Neurosciences, [1]Med. Univ. of South Carolina, Charleston, SC

Abstract: Chronic alcohol exposure is associated with morphological and structural changes in the cerebellum, yet little is known about its effects on synaptic transmission, plasticity, and excitability of Purkinje neurons, the sole output of the cerebellar cortex. Purkinje neuron dendritic spines and climbing fiber terminals show structural alterations in rats chronically exposed to alcohol and in alcohol-dependent humans, eyeblink conditioning, a cerebellar-dependent task associated with Purkinje neuron plasticity, is impaired. These findings suggest that repeated exposures to alcohol impacts synaptic transmission at inputs onto Purkinje neurons. To study this, we used a vapor inhalation model of chronic intermittent ethanol exposure (CIE) and treated adult C57Bl6J mice with four cycles of ethanol vapor. Each cycle was composed of four daily 16 hr episodes of ethanol vapor inhalation followed by an 8 hr withdrawal period. Whole-cell patch-clamp recordings were performed 72 hours following the last ethanol exposure. As CIE is known to affect the expression of NMDARs and to disrupt NMDAR-mediated forms of synaptic plasticity in other brain regions, we first evaluated the effects of CIE on parallel fiber NMDAR-dependent long term potentiation (PF-LTP). PF-LTP was induced by trains of PF stimulation (5 pulses at 200 Hz) repeated 300 times at 1 Hz. In control animals, the amplitude of PF-EPSCs measured 20 minutes after the induction protocol was significantly increased (133.2 ± 8.77 % of baseline) and a similar increase (132.7 ± 11.28 % of baseline) was observed in slices from CIE animals. Responses evoked by PF stimulation at different intensities also did not differ between control and treated animals (p=0.21, n=5-7). However PF-evoked firing threshold was decreased in CIE mice (-60.24 ± 1.69 mV in CIE vs -52.21 ± 2.55 mV, *p=0.0454*, n=4), suggesting that PC excitability is increased after CIE. We then evaluated the amplitude of NMDAR-mediated currents at climbing fiber to Purkinje neuron synapses. Following CIE exposure and withdrawal, the amplitude of these currents was enhanced (-106 ± 30.7 pA in CIE vs -51.17 ± 25.91 pA in controls, *p=0.045, n=5-8*), suggesting an upregulation of NMDARs at this synapse. This effect of CIE on NMDA receptor function is consistent with findings previously reported in other brain regions. Together, these results suggest that excitatory synaptic transmission onto cerebellar Purkinje neurons is affected by CIE treatment and may contribute to deficits in cerebellar-mediated behaviors observed following chronic exposure to ethanol.

Disclosures: P.A. Zamudio-Bulcock: None. **J.J. Woodward:** None.

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648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.14/G12

Topic: B.06. Synaptic Transmission

Support: NIH Grant AA025408
NIH Grant AA007456
NIH Grant GM068524

NIH Grant GM095970
NIH Grant AA006420
NIH Grant AA013498
NIH Grant AA015566

Title: Alcohol-induced neuroadaptation of IL-1 signaling at GABAergic synapses in the mouse prelimbic cortex

Authors: *F. P. VARODAYAN[1], M. Q. STEINMAN[1], T. D. DAVIS[2], S. A. WOLFE[1], T. NADAV[1], S. E. MONTGOMERY[1], W. B. KIOSSES[3], M. D. BURKART[2], A. J. ROBERTS[1], M. BAJO[1], M. ROBERTO[1]
[1]Dept. of Neurosci., The Scripps Res. Inst., La Jolla, CA; [2]Dept. of Chem. & Biochem., UCSD, La Jolla, CA; [3]La Jolla Inst. for Allergy and Immunol., La Jolla, CA

Abstract: The interleukin-1 (IL-1) system has emerged as a key regulator of the brain's response to alcohol. IL-1β expression is elevated in the brains of human alcoholics and ethanol-dependent rodents, and exogenous IL-1β treatment in rodents regulates inhibitory transmission in key addiction-related brain regions, promotes alcohol-induced neuroinflammation and potentiates withdrawal-induced anxiety. Moreover, the IL-1β neuroinflammatory response of ethanol-dependent rodents is associated with significant cognitive deficits. Therefore, here we investigated the mechanisms underlying alcohol-induced neuroadaptation of IL-1 signaling at GABAergic synapses in the prelimbic region of the medial prefrontal cortex, an area responsible for drug-seeking behaviors. We induced ethanol dependence by exposing C57BL/6J mice to the chronic intermittent ethanol vapor/2 bottle choice paradigm (CIE-2BC) and used whole-cell voltage-clamp electrophysiology to record spontaneous inhibitory postsynaptic currents in prelimbic cortex layer II/III pyramidal neurons. We found that IL-1β (50 ng/mL) reduced inhibitory input onto these cells in naïve mice, but enhanced it in ethanol-dependent mice. To uncover potential neuroadaptive mechanisms, we next examined whether these effects are sensitive to acute ethanol. In naïve mice, ethanol (44 mM) alone had no effect on GABA transmission, but IL-1β in the presence of acute ethanol increased GABA release (similar to the effects of IL-1β alone in dependent mice). Importantly, a 15 min washout of the acute ethanol application restored the ability of IL-1β to decrease GABA release in naïve mice. These interactions between the IL-1 system and acute and chronic ethanol involve both the PI3K/Akt and MyD88 intracellular cascades; Akt (200 nM MK-2206) or PI3K inhibition (50 µM LY294002) produced an IL-1β-induced increase in GABA release in naïve mice, while in dependent animals IL-1β's potentiation of GABA release was blocked by a MyD88 mimetic (AS-1, 50 µM) that prevented MyD88 recruitment to the IL-1 receptor complex. Potential chronic ethanol-induced changes in the expression of IL-1 signaling molecules and these two intracellular cascades are currently being assessed. Collectively, our results indicate that acute alcohol interacts with the IL-1 system, most likely by shifting its recruitment between the PI3K/Akt and MyD88 intracellular cascades, to regulate GABAergic synapses in the mouse prelimbic cortex, and that alcohol dependence produces neuroadaptation leading to a more persistent recruitment bias.

Disclosures: F.P. Varodayan: None. **M.Q. Steinman:** None. **T.D. Davis:** None. **S.A. Wolfe:** None. **T. Nadav:** None. **S.E. Montgomery:** None. **W.B. Kiosses:** None. **M.D. Burkart:** None. **A.J. Roberts:** None. **M. Bajo:** None. **M. Roberto:** None.

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648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.15/H1

Topic: B.06. Synaptic Transmission

Support: NIH R01 MH104641

Title: Acute osmotic stress produces differential effects on synaptic vs. paracrine signaling in oxytocinergic magnocellular neurons in the mouse paraventricular nucleus

Authors: *W. SHENG, S. W. HARDEN, C. J. FRAZIER
Dept. of Pharmacodynamics, Col. of Pharm., Univ. of Florida, Gainesville, FL

Abstract: Acute hypernatremia promotes natriuresis in part by increasing activity of oxytocinergic magnocellular neurons (OT-MCNs) in the hypothalamus that promote synaptic release of oxytocin (OT) from axon terminals in the neurohypophysis. Peripheral hypernatremia also blunts stress-induced activation of the hypothalamic-pituitary-adrenal axis via a mechanism that we believe is likely to depend on central paracrine (rather than synaptic) release of OT from magnocellular dendrites. Interestingly, prior work from other groups indicates that peripheral hypernatremia produces an increase in the concentration of circulating OT significantly more rapidly than it creates an increase in the concentration of central OT. The current project was designed to develop a better understanding of the underlying cellular mechanisms through which osmotic stressors may plausibly modulate both synaptic and paracrine release of OT from the same population of osmosensitive hypothalamic neurons, but with distinctly different temporal dynamics. Towards that end, we used the Cre-LoxP system to generate OT-reporter mice that express tdTomato in oxytocinergic neurons. Two-photon calcium imaging revealed that the dendrites of OT-MCNs are passive conductors, with robust activity dependent dendritic calcium influx that diminishes substantially with increasing distance from the soma. Further work revealed that acute osmotic stress (AOS) increases action potential frequency as observed in the soma via whole cell patch clamp recordings, and yet also substantially diminishes activity dependent calcium influx as observed in the distal dendrites. Indeed, we report that the effect of AOS on activity dependent calcium influx into distal dendrites is TTX insensitive, cell type (and compartment) specific, and bidirectional. Finally, we find AOS also reduces impact of distal glutamatergic inputs as observed in the soma, and suggest that other modulators may similarly regulate activity dependent dendritic release of oxytocin by modulating dendritic input resistance. Collectively, these results provide new insight into how osmotic stress differently

modulates synaptic vs. paracrine OT release from OT-MCNs in the mouse paraventricular nucleus.

Disclosures: W. Sheng: None. **S.W. Harden:** None. **C.J. Frazier:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.16/H2

Topic: B.06. Synaptic Transmission

Support: EMBO_LT_797_2012
HFSP_LT000830/2013
ERC-2013-CoG NeuroMolAnatomy

Title: NeuroLnc, a nuclear long non-coding RNA that regulates neuronal activity and development

Authors: *V. KLÜVER[1], S. KEIHANI[1], S. MANDAD[1,2], V. BANSAL[3], J. D. WREN[4], H. URLAUB[2], S. BONN[3], S. O. RIZZOLI[1], E. F. FORNASIERO[1]
[1]Neuro- and sensory physiology, Univ. Med. Ctr., Goettingen, Germany; [2]Clin. Chem. and Bioanalytical Mass Spectrometry, Univ. Med. Ctr. and Max Planck Inst. of Biophysical Chem., Goettingen, Germany; [3]Computat. Systems Biol., German Ctr. for Neurodegenerative Dis. (DZNE), Goettingen, Germany; [4]Biochem. & Mol. Biol. and Geriatric Med., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK

Abstract: Long noncoding RNAs (lncRNAs) are transcripts with lengths of >200 nucleotides that have been associated with numerous cellular processes, including X-chromosome inactivation, carcinogenesis and a wide range of developmental processes. The high incidence of lncRNAs in large genomes has been suggested to reflect the complexity of the underlying regulatory networks. Synaptic transmission is the quintessential example of a biological process that requires complex regulatory networks, and neurons express a large variety of lncRNAs. While several lncRNAs have been described in the nervous system, their molecular function in synaptic transmission has not been thoroughly explored. Thus, we designed a screening strategy based on a pHluorin assay to test the role of lncRNAs in synaptic vesicle exo-endocytosis. After an initial bioinformatic selection of lncRNAs, we tested the ten most promising candidates in our assay and found some of them to significantly affect neurotransmitter release. We termed the most interesting one among these “NeuroLnc”. NeuroLnc has a nuclear localization, it is highly neuron-specific and its expression is developmentally controlled. We used adeno-associated viruses to overexpress or downregulate NeuroLnc in hippocampal neurons, and found that its overexpression enhances calcium currents and favors neurite elongation, while its

downregulation produces the opposite effects. Moreover, *in utero* downregulation of NeuroLnc impairs the migration of neurons in developing mouse cortices. Using mass-spectrometry we identified several NeuroLnc interactors which included RNA-binding proteins as well as molecules implicated in neuropathology. We also studied the changes that NeuroLnc elicits at the transcriptome level and found several key changes in pathways related to neuronal development and transmission, suggesting that this lncRNA has pleiotropic effects on neuronal physiology. Our results reinforce the idea that molecules which are rapidly synthetized and degraded, such as RNAs, can contribute to the fine-tuning of neurons and underline the importance of lncRNAs for the regulation of the neuronal physiology.

Disclosures: V. Klüver: None. **S. Keihani:** None. **S. Mandad:** None. **V. Bansal:** None. **J.D. Wren:** None. **H. Urlaub:** None. **S. Bonn:** None. **S.O. Rizzoli:** None. **E.F. Fornasiero:** None.

Poster

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Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.17/H3

Topic: B.06. Synaptic Transmission

Support: NIH R01 NS40296

Title: Examining the role of *Drosophila* synaptotagmin 7 in synaptic transmission

Authors: *M. C. QUINONES-FRIAS[1], Z. GUAN[1], Y. AKBERGENOVA[1], T. LITTLETON[1,2]
[1]Picower Inst., [2]Biol. Dept., MIT, Cambridge, MA

Abstract: Synaptic communication dependents on proteins that sense calcium and drive SNARE-dependent exocytosis. Initially, release is rapid and synchronized with the action potentialand is mediated by the calcium sensor Synaptotagmin 1 (Syt1). This is followed by a slower calcium-dependent phase of release that occurs through a Syt1-independent mechanism. Recent evidence suggests the asynchronous release calcium sensor may be another member of the Synaptotagmin family, Syt7. However, Syt7 has also been suggested to mediate synaptic facilitation, synaptic vesicle recycling, and lysosomal fusion. It is unclear if Syt7 mediates multiple roles in neurotransmission or if one function may underlie the host of defects that have been identified in mouse models. To examine conserved roles of Syt7 in neurotransmission, we used the CRISPR-Cas9 system to generate null mutations in the *Drosophilasyt7*locus and to tag the endogenous gene with GFP. Endogenous GFP-tagged Syt7 was observed in both the pre- and post-synaptic compartment and found at multiple subcellular locations within synapses. One pool of Syt7 localized near active zones, while other pools of Syt7 co-localized with the membrane trafficking markers Arl8 (lysosomes) and Rab11 (endosomes). Mutants in *syt7*were fully viable and displayed no obvious motor defects. The most robust synaptic defect recorded at

neuromuscular junctions (NMJs) in *syt7*mutants was a 50% increase in evoked neurotransmitter release in response to single action potentials. In contrast, overexpression of Syt7 reduced evoked release, indicating Syt7 acts endogenously to suppress synchronous neurotransmission. *syt7*mutants also displayed reduced paired-pulse facilitation. During high frequency stimulation, evoked responses in *syt7*mutants depressed faster than controls, but maintained a larger recycling synaptic vesicle pool and a faster recovery of the pool following stimulation. Surprisingly, *syt1*/*syt7*double null mutants were viable through the larval stages and actually displayed more neurotransmitter release than *syt1*mutants alone, indicating there must be other calcium sensors for asynchronous release at *Drosophila*NMJs. Electron microscopy did not reveal any robust defects in synaptic vesicle distribution at synaptic boutons. Overall, our data indicate Syt7 is likely to act in several pathways that alter synaptic vesicle release and recycling that control vesicle availability during stimulation. In addition, other calcium sensor(s) must be present that trigger the residual release in the absence of both Syt1 and Syt7.

Disclosures: Z. Guan: None. **Y. Akbergenova:** None. **T. Littleton:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.18/H4

Topic: B.06. Synaptic Transmission

Title: Reintroduction of synapsin II in knockout mice using neonatal viral injections

Authors: *R. SCHWARK, R. ANDRADE, M. BYKHOVSKAIA
Wayne State Univ. Sch. of Med., Detroit, MI

Abstract: The synapsins (Syn) are a family of presynaptic phosphoproteins that modulate neurotransmitter release via reversible association with synaptic vesicles. Deficiency in synapsins I or II results in an epileptic phenotype in mice. By employing whole-cell recordings from hippocampal slices, our lab has previously shown that CA1 pyramidal neurons of SynII-KO mice exhibit increased frequency of spontaneous excitatory currents (sEPSCs), and a lower threshold of epileptiform activity produced by the epileptogenic agent 4-aminopyridine (4-AP). Here we utilize neonatal viral injections to balance the neuronal hyperexcitability in SynII-KO mice via the expression of SynII. We took advantage of injections at P0, when the ependymal lining of the ventricles is immature and permeable to adeno-associated viruses (AAVs), and cerebrospinal fluid can disseminate AAVs throughout the entire brain. Neonatal SynII-KO pups were anesthetized and injected with AAV1-*Syn2-EGFP* into the lateral ventricles in order to induce brain-wide rescue of Syn II. Expression of SynII-GFP was confirmed using epi-fluorescence microscopy in brain slices obtained from two and three-week old mice. Using whole-cell recordings from hippocampal slices derived from injected mice, we show that SynII

transfection significantly reduced sEPSC frequency in CA1 pyramidal neurons to the level observed in wild-type slices. These results demonstrate that global re-expression of SynII at P0 can robustly reduce synaptic hyperexcitability. This approach opens the avenue for employing neonatal injections to investigate the molecular and cellular pathways that govern hyperexcitability in the SynII-deficient brain.

Disclosures: R. Schwark: None. **R. Andrade:** None. **M. Bykhovskaia:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.19/H5

Topic: B.06. Synaptic Transmission

Support: R01GM112715

Title: Effects of general anesthesia on cortical neuronal activity in adults and neonates

Authors: *D. P. AKSENOV, M. MILLER, C. DIXON, A. WYRWICZ
NorthShore Univ. HealthSystem, Evanston, IL

Abstract: Volatile general anesthetics are used commonly in adults and children, but the dynamics of single unit firing throughout the anesthesia process have not been well studied *in vivo*. The process of general anesthesia comprises three main phases: the initial induction of decreased neuronal activity, the sustained plateau phase and the recovery phase. Characterizing the activity of single units throughout these phases requires stable, continuous recording of single neurons in the awake, anesthetized and recovery states, which represents a challenge for most animals models. Developing a better understanding of the neuronal changes that underlie the anesthesia process is important for comparing the effects of different anesthetics and the mechanisms through which they interact with the brain. Here we investigate how different anesthetics and their concentrations impact cortical single unit activity in adult and neonate rabbits. Neonate (6 days old) or adult Dutch-Belted rabbits were chronically implanted with electrodes in the whisker barrel cortex. The multiple signals from the microwires were fed through a miniature preamplifier to a multichannel differential amplifier system (Neuralynx Inc, Bozeman, Montana, USA). The signals were amplified, band-pass-filtered (300Hz to 3 kHz), and digitized (32 kHz/channel) using a Neuralynx data acquisition system. Unit discrimination was performed offline using threshold detection followed by a cluster analysis of individual action potential wave shapes using Neuralynx analysis software. Single unit firing was recorded continuously before, during and after delivery of two commonly-used volatile general anesthetics: isoflurane or sevoflurane. As anesthesia protocols often involve delivery over a wide range of hyperoxic mixtures, delivery of volatile anesthetics was tested in air as well as in

combination with 80% oxygen. Our results indicated that the single unit activity decreased during anesthetic delivery in a concentration-dependent manner. Although sevoflurane and isoflurane belong to the same class of general anesthetics, they produced considerably different levels of neuronal suppression during anesthesia as well as different rates of neuronal recovery. Furthermore, their effects were different in neonates and adults. Our results highlight how characterizing the temporal behavior of single units before, during and after anesthesia can provide detailed information about the impact of anesthetics on neuronal activity in specific brain regions.

Disclosures: D.P. Aksenov: None. **M. Miller:** None. **C. Dixon:** None. **A. Wyrwicz:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.20/H6

Topic: B.06. Synaptic Transmission

Support: NIH Grant EY028212

Title: Subanesthetic-dose ketamine induces sustained cortical disinhibition through downregulation of neuregulin-1/ErbB4 signaling

Authors: *X. QIAO, C. NGUYEN, X. XU
Dept. of Anat. and Neurobio., Univ. of California Irvine, Irvine, CA

Abstract: Ketamine is a non-competitive antagonist of N-methyl-D-aspartate receptors and has been used for anesthesia. A finding is that a single low dose of ketamine can elicit a rapid antidepressant action with sustained effects lasting for 10 - 14 days. Ketamine can modulate circuit excitation and inhibition in the cortex and alter the neurochemistry of parvalbumin (PV)-expressing neurons. Ketamine may mediate its behavioral effects through neural plasticity processes. As Neuregulin-1 (NRG1) and its receptor ErbB4 are involved in visual cortical plasticity (Sun et al., 2016), we hypothesize that ketamine treatment may activate visual cortical plasticity through NRG1 signaling in PV neurons. We study the effects of subanesthetic-dose ketamine (10 mg/kg) on synaptic circuit connections of excitatory neurons and PV neurons in layer 2/3 of mouse visual cortex and test whether NRG1/ErbB4 signaling is involved in this process. Electrically evoked inhibitory postsynaptic currents (IPSCs) recorded in excitatory neurons in adult C57/B6 mice without ketamine treatment (666 ± 165 pA, n=9 cells) were stronger than those recorded in ketamine treated mice at 24 hours after systemic injection (401 ± 60 pA, n=12 cells) and PV-Cre; ErbB4$^{flx/flx}$ mice with and without ketamine treatment (226 ± 31 pA, n=10 cells and 268 ± 38 pA, n=13 cells, respectively). Bath applied NRG1 increased IPSCs in excitatory neurons from mice at 24 hours after ketamine injection (NRG1/baseline ratio: 1.97

± 0.22, n=12 cells), but not in excitatory neurons from wild-type mice without ketamine treatment (NRG1/baseline ratio: 0.97 ± 0.06, n=9 cells) or in PV-Cre; ErbB4$^{flx/flx}$ mice with and without ketamine treatment (NRG1/baseline ratio: 1.04 ± 0.05, n=10 cells and 0.99 ± 0.04, n=13 cells, respectively). We mapped local excitatory inputs to PV neurons by laser scanning photostimulation via glutamate uncaging. Photostimulation-induced excitatory postsynaptic responses are not significantly influenced by bath applied NRG1 in PV neurons from PV-Cre; Ai9 mice without ketamine treatment. However, in ketamine treated PV-Cre; Ai9 mice at 24 hours, 48 hours and 72 hours after systemic injection, bath applied NRG1 significantly increased excitatory postsynaptic responses of PV neurons, supporting ketamine-induced downregulation in PV neuronal NRG1/ErbB4 signaling. Together, our results indicate that ketamine treatment modulates NRG1/ErbB4 signaling and reduces excitatory inputs to local PV neurons, which in turn decreases PV inhibitory inputs to excitatory neurons. These findings suggest subanesthetic-dose ketamine can alter circuit excitation / inhibition in adult cortex to better treat amblyopia.

Disclosures: X. Qiao: None. **C. Nguyen:** None. **X. Xu:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.21/H7

Topic: B.06. Synaptic Transmission

Support: NIH Grant NS084473 (DJ)
NARSAD Grant 26382 (CSK)

Title: Effects of ketamine and its metabolite 2R,6R-hydroxynorketamine on synaptic transmission and dendritic properties in dorsal CA1 neurons

Authors: *C. KIM, D. JOHNSTON
The Univ. of Texas At Austin, Austin, TX

Abstract: The limbic system is an integral brain region that underlies the action of depression and antidepressants. Growing evidence suggests that glutamatergic and GABAergic dysfunction may contribute to major depressive disorders. A sub-anesthetic dose of ketamine, a rapid and sustained antidepressant, is known to increase glutamine/glutamate and gamma-aminobutyric acid (GABA) releases within 30-40 min in the medial prefrontal cortex of depressed patients. We previously demonstrated that reduced expression of the HCN1 (Hyperpolarization-activated, Cyclic nucleotide gated, Non-selective cation) subunit of h-channels in the dorsal CA1 region leads to anxiolytic- and antidepressant-like effects in normal rats. When rats are exposed to chronic unpredictable stress (CUS), expression of HCN1 and I_h are upregulated in the perisomatic region of dorsal, but not ventral CA1 region/neurons of the hippocampus. We,

therefore, tested whether ketamine counteracts the shunting effects of I_h in dorsal CA1 neurons. We found a significant increase in synaptically evoked excitatory and inhibitory postsynaptic potentials (eEPSPs and eIPSPs) in the soma and dendrites of dorsal CA1 neurons following ketamine or 2R,6R-hydroxynorketamine (HNK) application. We also found that dendritic, but not somatic, h-measurements (R_{in} and f_R) were significantly changed at depolarizing membrane potentials (ranging from -68 mV to -83 mV) following ketamine or 2R,6R-HNK application (in the presence of AP5). These effects of ketamine on h-measurements suggested a reduction in I_h, which was distance-dependent along the somatodendritic axis of dorsal CA1 neurons. These findings represent NMDA-independent action of ketamine or 2R,6R-HNK on synaptic transmission and dendritic properties in dorsal CA1 neurons.

Disclosures: C. Kim: None. **D. Johnston:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.22/H8

Topic: B.06. Synaptic Transmission

Title: Human induced pluripotent stem cell (hiPSC) - derived motor neurons co-cultured with primary astrocytes exhibit functional network sensitivity to botulinum neurotoxin

Authors: *B. J. BLACK, J. J. PANCRAZIO
The Univ. of Texas At Dallas, Dallas, TX

Abstract: Botulinum neurotoxin (BoNT) is the most toxic protein known to man. BoNTs act presynaptically to prevent neurotransmitter release, causing sustained paralysis, and, at sufficiently high doses, death by asphyxiation. Currently, there are no proven clinically effective treatments for reversing intoxication. The gold standard method for BoNT quantification is based on the mouse lethality assay which low-content, and incurs high animal burdens. These disadvantages have driven the development of alternative molecular, cellular, and tissue-based approaches. Substrate-integrated microelectrode arrays (MEAs) enable long-term non-invasive interrogation of phenotypic network activity in vitro. Recent technological advances have enabled more rapid neurotoxicological assessments via elecrtrophsyiological measures, but this approach is still limited due to the availability of physiologically relevant cells. Here, we report exploratory studies regarding BoNT/A sensitivity using a commercially available hiPSC motor neuron (hiPSC MN) - astrocyte co-culture model.
Methods: Astrocytes were isolated and sub-cultured from primary embryonic whole-brains at a density of 50,000 cells/cm2. hiPSC MNs were provided by BrainXell, Inc. and cultured as specified by the vendor. hiPSC MNs were seeded at 100,000 cells/cm2 on astrocyte feeder layers three days following astrocyte culture. Spontaneous network activity was monitored using the

Axion Maestro multi-well MEA recording system. Extracellular action potentials were defined as band pass filtered (300 - 5000 Hz) continuous data crossings of a 5.5σ adaptive threshold. Network activity was quantified as a combination of network bursting rates and cross-channel synchrony. 100 ng/ml BoNT/A was added on DIV 16 and recordings were collected every 24 hours following BoNT/A addition.
Results: ChAT staining of homogeneous hiPSC MN cultures confirmed a highly purified homogeneous motor neuron population. Dual GFAP and β-III tubulin staining of astrocyte cultures confirmed high purity of GFAP positive astrocytes (>95%). Network activity, consistent with formation of functional synapses, emerged following 7 DIV. No network activity was observed in homogeneous control cultures of hiPSC MNs. BoNT/A (100 ng/ml) induced significant reduction in network bursting rate and synchrony following 24 h incubation. This reduction in network activity persisted at least 7 days following BoNT/A washout. No modulation of intrinsic spontaneous activity was observed in homogeneous control cultures of hiPSC MNs.

Disclosures: B.J. Black: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BrainXell. **J.J. Pancrazio:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BrainXell.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.23/H9

Topic: B.06. Synaptic Transmission

Support: Sponsored Research Agreement from Blackthorn Therapuetics

Title: Characterization of the nociceptin system in neural circuits underlying highly palatable food intake as a model of reward

Authors: J. A. HARDAWAY[1], K. BOYT[2], W. J. MARTIN[3], T. L. WALLACE[3], *T. KASH[4]
[1]Pharmacology, Ctr. for Alcohol Studies, Univ. of North Carolina at Chapel Hill, CHapel Hill, NC; [2]UNC Chapel Hill, Chapel Hill, NC; [3]Blackthorn Therapeut., San Francisco, CA; [4]UNC-Chapel Hill, Chapel Hill, NC

Abstract: Nociceptin/orphanin FQ (N/OFQ) and its receptor (NOP) are widely distributed in cortical and subcortical brain regions and are involved in multiple functions including stress modulation and reward processing. Previous studies from our group and others have shown that antagonists for NOP can specifically reduce consumption of highly palatable food, while maintaining overall food intake, highlighting the role of the N/OFQ system in mediating rewarding processes involved in feeding behavior. In the current study, we examined the

mechanism of action of a novel and selective NOP antagonist, BTRX-246040, and aimed to confirm and extend these earlier findings by characterizing the neural substrates and circuitry underlying palatability-induced hyperphagia. We first assessed target engagement using a whole cell slice physiology approach in C57BL/6J mice. Our initial studies were focused in the Central Nucleus of the Amygdala (CeA), as we recently found that pre-pronociceptin (gene precursor for N/OFQ) expressing neurons in the CeA play a key role in regulation of palatable food intake. Consistent with previous studies, we found that bath application of N/OFQ, the endogenous peptide agonist for NOP, led to a reduction in evoked GABAergic transmission in the CeA using whole cell electrophysiology. The reduction in GABAergic neurotransmission was blocked by pre-application of BTRX-246040 further demonstrating the specificity of this effect to NOP. We then sought to identify brain-wide neural circuits that drives preference for palatable food consumption, and the impact BTRX-246040 may have on them using a whole-brain c-fos imaging and analysis approach, iDISCO-CLEARMAP. In these experiments, we aim to identify differential brain activity patterns associated with the consumption of highly-palatable food and regular chow, and to investigate the effects BTRX-246040 has on these patterns. Furthermore, we will examine how NOP antagonism alters the activity of both pre-pronociceptin containing neurons and NOP-containing neurons using genetically engineered mouse lines coupled to confocal imaging. The results of these studies will highlight the circuit mechanisms by which BTRX-246040 alters consumption of highly palatable food and provide insight into the role of the N/OFQ system in reward processes underlying obesity and binge eating disorder.

Disclosures: J.A. Hardaway: 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.; Blackthorn Therapeutics. **K. Boyt:** 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.; Blackthorn Therapeutics. **W.J. Martin:** A. Employment/Salary (full or part-time):; Blackthorn Therapeutics. **T.L. Wallace:** A. Employment/Salary (full or part-time):; Blackthorn Therapeutics. **T. Kash:** 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.; Blackthorn Therapeutics.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.24/H10

Topic: B.06. Synaptic Transmission

Support: Studies funded by BlackThorn Therapeutics

Title: Modulation of ventral tegmental area (VTA) neurons by the nociceptin/orphanin fq (N/OFQ) system

Authors: *J. R. DRISCOLL[1], E. B. MARGOLIS[2], T. L. WALLACE[3], W. J. MARTIN[4]
[1]Univ. of California San Francisco, San Francisco, CA; [2]Neurol., UCSF, San Francisco, CA; [3]BlackThorn Therapeut., San Francisco, CA; [4]Blackthorn Therapeut., San Francisco, CA

Abstract: Nociceptin/Orphanin FQ (N/OFQ) is a non-opioid, stress-induced neuropeptide that has been associated with disorders involving altered reward processing and motor function. One hypothesis for the broad emotional and behavioral influence of N/OFQ is through the modulation of dopamine signaling. N/OFQ and its cognate receptor, OLR1, are highly enriched in mesocortical and mesolimbic pathways, and intracerebroventricular injections of N/OFQ result in the inhibition of dopamine in the striatum, nucleus accumbens, and the ventral tegmental area (VTA). To better understand how N/OFQ may influence physiological mechanisms of dopamine signaling in cortical and limbic brain regions we use whole cell electrophysiology in acute midbrain slice preparations from rat to characterize the synaptic actions of N/OFQ on VTA neurons. In this study, neurons were maintained in voltage clamp mode at -60 mV and changes to membrane current in response to N/OFQ (1 nM to 10 M) were measured in both tyrosine hydroxylase (TH)+ and TH- neurons sampled throughout the VTA. Consistent with the literature, we found that N/OFQ was inhibitory, causing outward currents, in both TH+ and TH- VTA neurons. We did not observe a significant difference in the concentration response curves between TH+ and TH- neurons. The resulting dose response curve for N/OFQ yielded an EC_{50} < 5 nM, substantially lower than concentrations used in previous behavioral experiments in rodents. We also observed that repeated application of high dose N/OFQ (> 100 nM) was associated with a marked decrease in current response, a result that is consistent with desensitization. In contrast, repeated application of low dose N/OFQ (10 nM) consistently induced a similar current response. To test the specificity of responses to N/OFQ (10 nM), we bath applied a selective OLR1 antagonist, BTRX-246040 (100 nM), to confirm N/OFQ-responsive neurons. BTRX-246040 consistently blocked the inhibitory outward current activated by N/OFQ (n=6, $p<0.01$). The data from these studies provide an electrophysiological characterization of the inhibitory effect of N/OFQ on VTA neurons and demonstrate the selective antagonist activity of BTRX-246040 in this population of cells. These results extend our understanding of the involvement of N/OFQ within key circuits implicated in many neurobehavioral disorders and support the development of N/OFQ antagonists as novel therapeutics.

Disclosures: **J.R. Driscoll:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. **E.B. Margolis:** 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.; BlackThorn Therapeutics. **T.L. Wallace:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. **W.J.**

Martin: A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.25/H11

Topic: B.06. Synaptic Transmission

Support: PICT 2013-2202 and 2016 3624 from Agencia Nacional de Promoción Científica y Tecnológica (ANPCYT)
UBACYT 01/Q666 (20020130100666BA) from University of Buenos Aires.

Title: Histamine significantly increases ASIC-1a contribution to excitatory synaptic transmission at the calyx of Held

Authors: *O. D. UCHITEL, C. GONZALEZ-INCHAUSPE
IFIBYNE UBA CONICET, Buenos Aires 1428, Argentina

Abstract: Acid-sensing ion channels (ASICs) regulate synaptic activities and play important roles in neurodegenerative diseases. We found that homomeric ASIC-1a channels are expressed in neurons of the medial nucleus of the trapezoid body (MNTB) of the auditory system in the CNS. During synaptic transmission, acidification of the synaptic cleft, presumably due to the co-release of neurotransmitter and H^+ from synaptic vesicles, activates postsynaptic ASIC-1a channels, generating synaptic currents (ASIC-SCs) that add to the glutamatergic excitatory postsynaptic currents (EPSCs). Here we report that neuromodulators like histamine (0.1-1mM) potentiate ASIC-SCs up to 84 ± 4 % and that natural products like lactate and spermine potentiate ASIC-SCs in an additive form up to 221 ± 18 %, such that excitatory ASIC synaptic currents as well as the associated calcium influx became significantly large and physiologically relevant. We show that potentiated ASIC currents by endogenous neuromodulators are capable of supporting synaptic transmission in the absence of glutamatergic EPSC. Furthermore, at high frequency stimulation, ASIC-SCs contribute to diminish short term depression (STD) and their contribution is even more relevant at early stages of development. Since ASIC channels are present in almost all type of neurons and synaptic vesicles content is acid, the participation of protons in synaptic transmission and its enhancement by endogenous substance could be a general phenomenon across the central nervous system.

Disclosures: O.D. Uchitel: None. **C. Gonzalez-Inchauspe:** None.

Poster

648. Synaptic Transmission: Modulation: Mechanisms of Action

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 648.26/H12

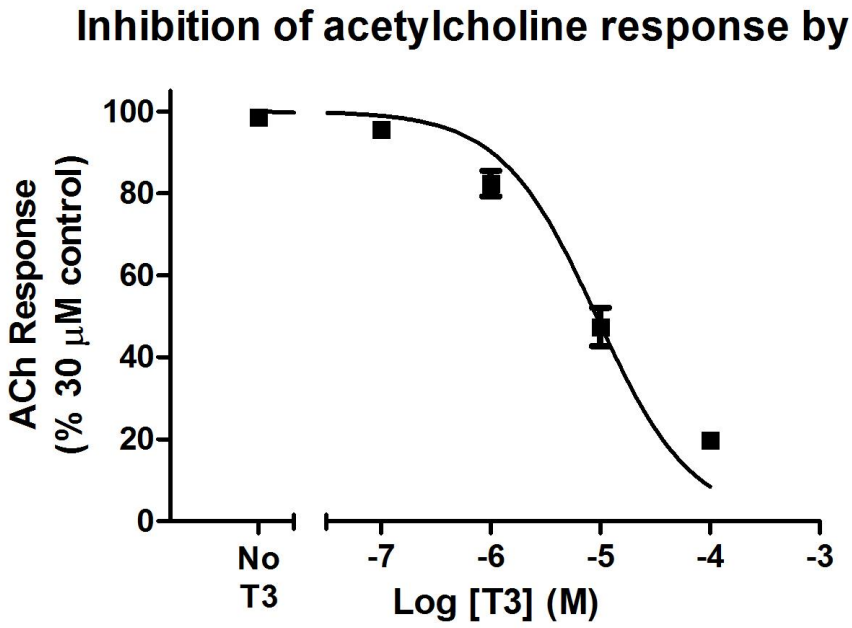
Topic: F.03. Neuroendocrine Processes

Support: NSF Grant MCB1330728

Title: Effects of thyroid hormone, pregnenolone sulfate and pH on function of nicotinic acetylcholine receptors

Authors: S. X. MOFFETT, E. A. KLEIN, G. BRANNIGAN, *J. V. MARTIN
Ctr. for Computat. & Integrative Biol., Rutgers Univ., Camden, NJ

Abstract: Historically, thyroid hormones were thought to have exclusively genomic actions in adults, with no short-term signaling effects, but recent evidence contradicts this. The thyroid hormone 3, 3',5-triiodothyronine (T3) localizes in adult brain noradrenergic centers and projection sites. T3 affects sleep after microinjection into the median preoptic nucleus of adult male rats. It has neurotransmitter-like, inhibitory effects on the GABA-A receptor, a pentameric ligand-gated ion channel (pLGIC). The neurosteroid pregnenolone sulfate (PS) has a similar size and structure to T3, and inhibits activity of the GABA-A receptor as well. Another pLGIC, the nicotinic acetylcholine receptor (nAChR), is highly concentrated in the sea ray *Torpedo californica*'s electric organ. We extracted *Torpedo* nAChRs and reconstituted functional channels in asolectin (soybean) lipids. We injected resuspended nAChRs into *Xenopus* oocytes and performed two-electrode voltage clamping (TEVC) studies to demonstrate modulatory effects on nAChR response to acetylcholine due to T3/PS binding or different pH environments. Here we show an inhibitory effect on ion flux through the nAChR with increasing concentration of co-administered T3, similar to the inhibitory effect of PS. We also show a direct relationship between positive modulation of the nAChR channel and increasing pH in perfusion solutions (n=3, per condition). Finally, we show that this pH relationship has complex effects on desensitization when the channel is inhibited by T3 or by PS. The effect due to pH, the inhibitory effects due to T3 and PS, and the differing relationship between the pH and each of the ligands' effects may implicate charged residues within the transmembrane domain of the nAChRs in both ligand binding and channel conductance.



Disclosures: S.X. Moffett: None. **E.A. Klein:** None. **G. Brannigan:** None. **J.V. Martin:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.01/H13

Topic: B.11. Glial Mechanisms

Title: Global transcriptome analysis reveals genes and signaling pathways regulated by lactate in cortical neurons

Authors: *M. B. MARGINEANU, H. FIUMELLI, P. J. MAGISTRETTI
BESE, King Abdullah Univ. of Sci. and Technol., Thuwal, Saudi Arabia

Abstract: Lactate, a product of aerobic glycolysis in astrocytes, is required for memory formation and consolidation, and has recently emerged as a signaling molecule for neurons and various cell types of peripheral tissues. In particular lactate stimulates mRNA expression of a few plasticity-related genes. Here, we describe a RNA-Seq study that unravels genome-wide transcriptomic responses to this energy metabolite in cortical neurons. Our results show that mRNA expression of 4999 genes was modulated after 1h, 6h, and 24h of lactate treatment (FDR<0.05). Among these, the expression of 20 immediate-early genes involved in the MAPK signaling pathway and in synaptic plasticity was increased following 1h of lactate stimulation.

This effect was dependent on NMDA receptor activity since it was prevented by pre-treatment with MK-801. Comparison with published datasets showed that a significant proportion of genes modulated by lactate were similarly regulated by a synaptic NMDA receptors activation protocol known to result in upregulation of pro-survival and downregulation of pro-death genes. Remarkably, transcriptional responses to lactate were reproduced by NADH suggesting a redox-dependent mechanism of action. Longer-term gene expression changes observed after 6h and 24h of lactate treatment, affected genes involved in regulating neuronal excitability, glutamatergic transmission and genes coding for proteins localized at synapses. Gene set enrichment analyses performed with ranked lists of expressed genes revealed effects on molecular functions involved in epigenetic modulation, and on processes relevant to sleep physiology and behavioral phenotypes such as anxiety and hyperactivity. Overall, these results strengthen the notion that lactate effectively regulates activity-dependent and synaptic genes, and highlight new signaling effects of lactate in plasticity and neuroprotection.

Disclosures: M.B. Margineanu: None. **H. Fiumelli:** None. **P.J. Magistretti:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.02/H14

Topic: B.11. Glial Mechanisms

Support: CRG grant from KAUST-EPFL Alliance for Neuro-inspired High Performance Computing
EPFL / ETH Board funding to the Blue Brain Project
NCCR, Synapsy and the Prefargier Foundation to PJM

Title: Unexpected diversity of metabolic regulatory profiles revealed by cascade tuning in a computational model of the neuro-glio-vasculature

Authors: *J. S. COGGAN[1], P. SHICHKOVA[2], D. KELLER[3], H. MARKRAM[4], F. SCHUERMANN[5], P. J. MAGISTRETTI[6]
[1]Blue Brain Project / EPFL, Geneva, Switzerland; [2]Blue Brain Project, EPFL, Geneva, Switzerland; [3]Blue Brain Project, Brain Mind Institute, EPFL, Lausanne, Switzerland; [4]EPFL, Blue Brain Project, Lausanne, Switzerland; [5]Campus Biotech, EPFL - Blue Brain Project, Geneva, Switzerland; [6]Biol. and Envrn. Sci. and Engin. Div., King Abdullah Univ. of Sci. and Technol. (KAUST), Thuwal, Saudi Arabia

Abstract: Intracellular metabolic cascades triggered by stimulation of second messenger-coupled cell membrane-bound receptors are responsible for numerous biological functions including the regulation of energy supply to the brain. This complex network of biochemical

reactions including cAMP-dependent enzymes, glycogenolysis, glycolysis, and other downstream processes are regulated at various points. Using an atlas-based, data-driven computational model of the biochemical reactions contained within the neuro-glio-vascular ensemble (NGV), we demonstrate that the chain reaction of enzymes and metabolites forms a dynamical system, the components of which may exhibit hysteretic trajectories and shift phases in a concentration-dependent manner. The various metabolites and enzymes may also display non-linear, dose-dependent interdependencies. These cascade profiles can be tuned by adjusting individual components such as metabolite concentrations or enzyme kinetics and optimized for a desired outcome. We propose that "cascade tuning" with a broad diversity of previously unexploited regulatory options could be important to cellular functions, as well as a useful research tool for studying cell metabolism.

Disclosures: J.S. Coggan: None. **P. Shichkova:** None. **D. Keller:** None. **H. Markram:** None. **F. Schuermann:** None. **P.J. Magistretti:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.03/H15

Topic: B.11. Glial Mechanisms

Title: Contribution of astrocytic Connexin 43 in energy homeostasis

Authors: *F. GUILLEBAUD, K. POIROT, B. LEBRUN, M. DALLAPORTA, S. RAMI, J.-D. TROADEC
Aix Marseille Univ., Marseille, France

Abstract: The metabolic syndrome, which comprises obesity and diabetes, is a major public health issue and consequently the understanding of energy homeostasis control remains an important worldwide concern. The homeostatic regulation of energy balance is under the control of specific neuronal networks, located mainly in the hypothalamus (hypth) and the dorsal vagal complex (DVC). These structures integrate nutritional, humoral and nervous information arising from the periphery. Glial cells contribution to balance regulation has been poorly studied until recently and the role of gliotransmitters in these mechanisms warrants further investigations. In the present study, we sought to evaluate the involvement of astrocytic Connexin 43 (Cx43) hemichannels and the release of subsequent gliotransmitters in energy balance regulation. We showed that Cx43 is strikingly expressed in the hypth and DVC while Cx43 was mostly found in close apposition to synapses located through pre-synaptic Bassoon presence. Then, we used intracerebroventricular injection of TAT-Gap19, a peptide that specifically blocks Cx43 hemichannels activity. We reported a strong decrease of food intake upon TAT-Gap19 treatment, without further alteration of energy expenditure. Moreover, TAT-Gap19 induced the activation

of prototypic anorexigenic neurocircuitries as attested the expression of the immediate early gene c-Fos. Altogether, these results suggest a tonic delivery of orexigenic molecules associated with astrocytic Cx43 hemichannel activity. To further decipher the role of astrocytic Cx43 in energy homeostasis, we generated a mouse line exhibiting a conditional deletion of Cx43 gene in astrocytes of hypth and/or DVC. The deletion of Cx43 in astrocytes was achieved by crossing Cx43 floxed mice with mice harbouring the Cre transgene under the control of GFAP transcriptional elements. The Cre activity was dependent on ERT2 receptor and induced in adult mice by endoxifen administration. Endoxifen was administered within the 3rd and/or 4th ventricle(s) to target the hypth and/or the DVC respectively. The validity of this approach was confirmed by using td-Tomato knock-in mice and local quantification of Cx43 gene expression after Cre recombinase induction. Food intake, energy expenditures and locomotor activity were recorded on this unique Cx43 specific KO model to characterize the whole influence of Cx43 in energy homeostasis. The susceptibility of the conditional KO mice to high fat diet-induced obesity is under investigation. Collectively, these results suggest that glial Cx43 is essential for homeostatic regulation of energy balance and could open new therapeutic avenues.

Disclosures: F. Guillebaud: None. **K. Poirot:** None. **B. Lebrun:** None. **M. Dallaporta:** None. **S. Rami:** None. **J. Troadec:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.04/H16

Topic: B.11. Glial Mechanisms

Support: NIMH Grant MH-094268
NIMH Grant MH-083728
The Brain and Behavior Research Foundation Grant

Title: Metabolic changes in astrocytes: Implications for psychiatric disorders

Authors: *Y. JOUROUKHIN, A. V. SHEVELKIN, L. NUCIFORA, C. TERRILLION, O. MYCHKO, F. NUCIFORA, M. PLETNIKOV
Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Metabolic alterations and mitochondrial dysfunction have been described in patients with major psychiatric disorder. Astrocytes provide metabolic support for neurons and regulate synapse formation and neurotransmission. We studied the role of *NPAS3* (Neuronal PAS domain protein 3), a transcriptional factor highly expressed in astrocytes, in regulation of mitochondria functions. We evaluated cognitive outcomes using trace fear conditioning test; quantified the density of parvalbumin- and glutamate decarboxylase-positive pre-synaptic boutons on

pyramidal neurons of the frontal cortex layer 2/3 as well as performed RNA-seq analyses of hippocampal samples of mice with astrocyte-specific deletion of Npas3 (Npas3 KO). In addition, we evaluated mitochondrial function and measured glutamate and lactate production in Npas3 KO primary astrocytes. Our results show that learning and memory deficit in mice with astrocyte-specific deletion of *Npas3* accompanied by decreased density of parvalbumin-positive inhibitory neurons in prefrontal cortex. Moreover, we found that parvalbumin-positive neurons have reduced glutamate decarboxylase - immunoreactivity in their presynaptic boutons on pyramidal excitatory neurons. Remarkably, *Npas3* deletion was also associated with a 40-fold decrease in expression of the *Solute Carrier Family 25, Member 18* (*Slc25a18*) and decreased levels of its protein product, the mitochondrial glutamate carrier 2 (GC2). Reduced expression of GC2 resulted in decreased mitochondrial respiration and elevated secretion of glutamate by *Npas3* KO astrocytes. Our findings suggest a previously unknown role for *Npas3* in regulation of glutamate metabolism in astrocytes abnormalities in which could affect functioning of cortical inhibitory neurons, leading to cognitive impairment relevant to major psychiatric disorders.

Disclosures: A.V. Shevelkin: None. **L. Nucifora:** None. **C. Terrillion:** None. **O. Mychko:** None. **F. Nucifora:** None. **M. Pletnikov:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.05/H17

Topic: B.11. Glial Mechanisms

Title: Dissimilarities in energy-metabolizing enzymes between dorsal root ganglion neurons and Schwann cells

Authors: K. TRIYASAKORN[1], W. GAO[2], S. W. LEUNG[2], A. BHUSHAN[3], *J. C. LAI[4]
[1]Chem., [2]Civil and Envrn. Engin., Idaho State Univ. Col. of Sci. and Engin., Pocatello, ID; [3]Pharmaceut. Sci., Jefferson Col. of Pharmacy, Thomas Jefferson Univ., Philadelphia, PA; [4]Idaho State Univ. Col. of Pharm., Pocatello, ID

Abstract: Compartmentation in the metabolism of tricarboxylic acid (TCA) cycle intermediates, glutamate and GABA in mammalian brain has been established in the last two decades. The heterogeneity of expression of multiple enzyme systems in neurons and glial cells constitute one mechanism underlying the brain metabolic compartmentation. By contrast, the metabolic compartmentation of dorsal root ganglion (DRG) neurons and Schwann cells in the peripheral nervous system (PNS) is still inadequately defined. Three energy-metabolizing enzymes (lactate, glutamate, and malate dehydrogenases (LDH, GDH, and MDH)) were employed to investigate our hypothesis that metabolic differences between DRG neurons and Schwann cells exist. Activities of these enzymes were therefore studied employing the Clark and Lai assays.

Consistent with our hypothesis, the activities of these enzymes differed between the two cell types. GDH and LDH activities were much higher in Schwann cells than in DRG neurons while MDH activity was slightly higher in DRG neurons than in Schwann cells. Because our findings may have physiological/pathophysiological implications in normal and disease conditions in the PNS, further characterization of the metabolic properties of these PNS neural cells is warranted.

Disclosures: K. Triyasakorn: None. **W. Gao:** None. **S.W. Leung:** None. **A. Bhushan:** None. **J.C. Lai:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.06/H18

Topic: B.11. Glial Mechanisms

Support: SNTP Grant 5T32NS061764-09
NIH Grant 1R21NS091871

Title: The effect of BDNF signaling in VMH astrocytes on energy and glucose balance control

Authors: *D. AMEROSO, C. DULLA, M. RIOS
Neurosci., Tufts Univ. Sackler Sch. of Grad. Biomed, Boston, MA

Abstract: Central neural circuits critically regulate energy and glucose homeostasis. Neural networks within the hypothalamus receive and integrate peripheral energy status signals and respond by altering feeding behavior and energy expenditure to meet the nutritional demands of the animal. Brain-derived neurotrophic factor (BDNF) signaling in the ventromedial hypothalamus (VMH) is an essential component of these complex regulatory mechanisms. BDNF expression in the VMH is robustly induced in the fed state and activation of its receptor tyrosine receptor kinase B (TrkB) increases activity of VMH neurons and the anorexigenic tone and mediates glucose homeostasis. Importantly, reduced BDNF signaling in both mouse models and humans is associated with severe obesity and impaired glycemic control. In addition to its significant effects facilitating neuronal synaptic plasticity, BDNF has been shown to regulate astrocyte morphology and calcium signaling through activation of the TrkB splice variant TrkB.T1 in other brain regions. It is unclear whether VMH astrocytes are an essential substrate for actions of BDNF influencing metabolic function. Astrocytes are in contact with the blood supply and reciprocally communicate with neurons to regulate their activity. Thus, they are an excellent yet understudied candidate for sensing peripheral metabolic signals to accordingly shape the appropriate neuronal and metabolic responses. We hypothesize that VMH astrocytes are key regulators of energy and glucose balance, and that BDNF signaling in this cell population is critical for these effects. In support, preliminary data indicate that BDNF and energy status

dynamically regulate function and structural plasticity of VMH astrocytes to influence neuronal activity. Additionally, results show that VMH astrocytes exclusively express TrkB.T1 and that this receptor is required for proper energy balance control. As the VMH is a sexually dimorphic region, ongoing studies will assess whether these effects are influenced by sex. To ensure scientific rigor, all of the experiments involved appropriate use of controls, power analysis to determine cohort size and statistical analysis to determine significant differences. In total, our findings inform novel mechanisms involved in the regulation of central feeding circuits and provide a stepping-stone for identification of potential therapeutic targets in treating obesity and metabolic disorders.

Disclosures: D. Ameroso: None. **C. Dulla:** None. **M. Rios:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.07/I1

Topic: B.11. Glial Mechanisms

Support: AFSP SRG-0-088-1
CIHR MOP- 111022
ERA-NET NEURON (FRQ-S)

Title: Reduced astrocyte-oligodendrocyte gap junction coupling in the anterior cingulate cortex of depressed suicides

Authors: *A. TANTI, G. TURECKI, N. MECHAWAR
Douglas Mental Hlth. Univ. Inst., McGill Group For Suicide Studies, Montreal, QC, Canada

Abstract: Imaging studies have shown widespread changes in white matter integrity and brain connectivity in patients with major depressive disorder. This is in agreement with reports of altered oligodendrocyte densities and impaired myelin ultrastructure in human post-mortem studies as well as animal models of depression. Myelination of axons by oligodendrocytes is tightly regulated, notably by astrocytes, which establish gap junctions with oligodendrocytes through heterotypic coupling of astrocyte-specific (Cx30 and Cx43) and oligodendrocyte-specific (Cx32 and Cx47) connexins, allowing metabolic support to oligodendrocytes. Because decreased expression of astrocyte-specific connexin genes has been previously observed in the prefrontal cortex of depressed suicides, we ought to investigate if changes in myelin integrity associated with depression could be linked to abnormal oligodendrocyte-astrocyte coupling. Using well-characterized post-mortem samples from depressed suicides and matched controls, we used immunofluorescence and confocal microscopy to map and quantify the expression of Cx30 in oligodendrocytes and myelinated fibers, as well as along blood vessels of the anterior

cingulate cortex (ACC) grey matter. RNAseq data was used to screen for gap junction-related changes in gene expression and validated by quantitative PCR. We found that in the ACC, depressed suicides show a decreased expression of Cx32 and Cx47, both connexins involved in oligodendrocyte-astrocyte gap junction coupling, as well as decreased expression of several key mediators of gap junction assembly. These changes were associated with decreased Cx30 puncta mapping to oligodendrocytes, suggesting overall that depressed suicides display lower gap junction channel coupling between astrocytes and oligodendrocytes in the ACC grey matter. This may ultimately affect oligodendrocyte function and myelination within this brain area known to be critical for the regulation of mood and emotions. Given that glial pathology is a major hallmark of depression and suicide, understanding how glia-glia interactions shape oligodendrocyte function in health and disease may prove useful in understanding the neurobiological basis of mood disorders.

Disclosures: A. Tanti: None. **G. Turecki:** None. **N. Mechawar:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.08/I2

Topic: B.11. Glial Mechanisms

Support: NIH Grant 25A6333

Title: Nrf2 function in oligodendrocyte development and injury responses

Authors: *D. VERDEN[1], M. C. NEAL[1], C. SCHROEDER[2], P. S. HERSON[2], W. B. MACKLIN[1]
[1]Cell & Developmental Biol., [2]Pharmacol., Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: White matter injury is a crucial component of ischemic stroke pathophysiology. In addition to local neuronal death, ischemia damages oligodendrocytes, the myelin-producing cells of the central nervous system. Myelin loss drives inflammatory responses and causes secondary damage to myelinated axons connecting brain regions, inhibiting tissue recovery and increasing the scope of circuit dysfunction. Stroke susceptibility varies with age, and the juvenile period is characterized by greater stroke recovery than in neonates or adults. Previous work from our lab has shown that in juvenile mice, oligodendrocytes and myelin are resistant to ischemic injury. The juvenile period is the peak of central nervous system myelination, during which oligodendrocytes have increased metabolism demands that generate reactive oxygen species (ROS) byproducts. Active myelination requires increased antioxidant capacity, which we hypothesize may provide protection from ischemic injury in juvenile oligodendrocytes. RNA-

sequencing of acutely isolated juvenile and adult oligodendrocytes uncovered differential regulation of Nrf2, a master transcriptional regulator of oxidative stress response. Nrf2 is protective for several cell types following ischemia, and is known to protect oligodendrocytes from reactive oxygen species in other contexts, revealing a capacity for Nrf2-mediated ROS management in oligodendrocytes. We therefore investigated a potential dual role of Nrf2 both in oligodendrocyte development and ischemic response. Analysis of juvenile and adult brains revealed increased expression of Nrf2 in juvenile oligodendrocytes, and Nrf2 protein is upregulated during oligodendrocyte differentiation in primary oligodendrocytes. Preliminary evidence from an oligodendrocyte-specific Nrf2 knockout indicates that loss of Nrf2 causes reactive responses by NG2 cells. These results indicate that Nrf2 is developmentally regulated by oligodendrocytes and may play a role in oligodendrocyte lineage function. Additional characterization will determine the effect of Nrf2 on oligodendrocyte ROS management, as well as myelin production and maintenance.

Disclosures: D. Verden: None. **M.C. Neal:** None. **C. Schroeder:** None. **P.S. Herson:** None. **W.B. Macklin:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.09/I3

Topic: B.11. Glial Mechanisms

Support: KCL Start- up Grant
Wellcome Grant for David Attwell
European Leukodystrophy Association Grant

Title: TRPA1 channels regulate oligodendrocyte intermodal potassium conductance during ischaemia

Authors: *N. B. HAMILTON[1], M. CORNILLOT[2], M. KHARAGHANI[2], C. LA MACHE[2], K. KOLODZIEJCZYK[3], D. ATTWELL[4]
[2]Wolfson Ctr. for Age-Related Dis., [1]King's Col. London, London, United Kingdom; [3]Cardiac Services BC, Vancouver, BC, Canada; [4]Univ. Col. London, London, United Kingdom

Abstract: Oligodendrocytes wrap myelin around axons to speed neuronal transmission, provide trophic support and syphon away excess K^+ during burst firing of action potentials. These functions are crucial to normal brain function, and oligodendrocyte electrical conductance has the potential to limit or enhance action potential size and speed, as well as to limit the excitability of neurons. We have recently shown that raised extracellular K^+ concentrations that occur in ischaemia, can activate TRPA1 in oligodendrocytes (Hamilton et al., 2016). We now find that

TRPA1 activity can regulate internodal K^+ conductance through modulation of K^+ channel phosphorylation states and therefore the capacity for myelinating internodes to sequester K^+ from the axonal space during spontaneous action potentials. TRPA1-mediated inhibition of K^+ channels occurs during ischaemia, and can be prevented by blocking TRPA1 channels with HC 030031, ruthenium red or genetically removing TRPA1. These results suggest that oligodendrocyte TRPA1 channels may have an important role in regulating K^+ syphoning in the white matter and that this mechanism may play a role in ischaemia-evoked white matter changes.

Disclosures: N.B. Hamilton: None. **M. Cornillot:** None. **M. Kharaghani:** None. **C. La Mache:** None. **K. Kolodziejczyk:** None. **D. Attwell:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.10/I4

Topic: B.11. Glial Mechanisms

Support: China postdoctor fund

Title: Changes of myelin morphology and development in early stage of Alzheimer's disease mouse model

Authors: *Y. WU[1,2]
[1]Beijing City, China; [2]Inst. of Mental Hlth., Peking Univ., Beijing, China

Abstract: Alzheimer's disease (AD) is the most common cause to dementia and predicted to affect more than 35 million people by the end of 2050. In this study, we discovered alterations of myelin morphology in brain tissues of 2-month-old APP/PS1 mouse. Myelin sheath was thicker and distance between two nodes of Ranvier was shorter in APP/PS1 mouse. Oligodendrocytes, which was differentiated from oligodendrocytes progenitor cells (OPCs) and responsible for formation and maintenance of myelin sheath in central nervous system (CNS), was found developed in disordered in 2-month-old APP/PS1 mouse. Neuregulin-1 type III, which was critical for both oligodendrocytes development and central nervous system myelination, was found up-regulated in APP/PS1 mouse by western blots. Given together, this study indicated the changes of myelin sheath morphology and oligodendrocytes development in early stage of APP/PS1 mouse.

Disclosures: Y. Wu: None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.11/I5

Topic: B.11. Glial Mechanisms

Support: Multiple Sclerosis Society of Canada
Compute Canada

Title: Deep learning for cell-specific high-throughput quantification of oligodendrocyte ensheathment

Authors: *Y. XU[1], D. CHITSAZ[2], R. A. BROWN[2], J. P. ANTEL[3], T. E. KENNEDY[4]
[1]Neurol. and Neurosurg., Montreal Neurolog. Institute, McGill Univ., Montreal, QC, Canada; [3]Dept Neurol & Neurosurg., [2]McGill Univ., Montreal, QC, Canada; [4]Neurol. & Neurosurg., Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: Reducing myelin injury and enhancing myelin repair are central therapeutic objectives in reversing the progression of demyelinating diseases. Despite the unique structure of myelin, elaborated by oligodendrocytes (OL), quantifying the injury and repair responses of OLs on a large-scale still poses a significant methodological challenge to researchers. The lack of high-throughput systems capable of extracting cell-specific morphological information has impeded the screening and development of therapeutics for myelin diseases. In the present study, we established deep learning and classic algorithmic approaches that resolve this quantitative challenge by eliminating the time for image acquisition and analysis, while successfully matching human analytic quality. We first generated a classic algorithmic approach that used the basic morphological characteristics of OL ensheathments to assess the myelinating potential of OLs in nanofiber cultures. Next, we attempted to improve on this classic approach by combining automated imaging with deep learning techniques. Our deep learning approach employed a convolutional neural network that followed a "UNet" architecture to learn cell-specific information. During training, the UNet was presented with images appended to single nuclei masks so that the network could learn to associate ensheathments to specific cell nuclei rather than identify ensheathments globally. Through validation on cell-specific and whole-image levels, we demonstrate that both approaches could match the accuracy of human segmentations on several parameters, including length distributions and number of sheaths formed per cell. Overall, the combination of automated imaging and analysis has the potential to eliminate weeks of manual labor while offering a 5- and 20-fold increase in whole-well analytic speed for the UNet and classic algorithmic approaches respectively. Furthermore, since the task is highly parallelizable, the speed of analysis can be enhanced nearly indefinitely by employing additional computing workstations. By enhancing analytic speed without sacrificing analytic quality we

have developed a high-throughput system capable of quantifying single-cell ensheathments. This new technology permits the detection of nuanced differences associated with injury induction and repair to accelerate the development of therapeutics for myelin diseases.

Disclosures: Y. Xu: None. **D. Chitsaz:** None. **R.A. Brown:** None. **J.P. Antel:** None. **T.E. Kennedy:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.12/I6

Topic: B.11. Glial Mechanisms

Support: NIH/NICHD Grant HD076892
NIH/NICHD Grant HD090256
Metabolic Support UK

Title: Antisense oligonucleotides (ASOs) efficiently target glial cells and provide a novel therapeutic platform for demyelinating disorders

Authors: *B. POWERS[1], T. HAGEMANN[2], C. MAZUR[1], F. RIGO[1], A. MESSING[2], E. SWAYZE[1]
[1]Neurosci. Drug Discovery, Ionis Pharmaceuticals, Carlsbad, CA; [2]Dept. of Neuropathology and Waisman Ctr., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Antisense oligonucleotide (ASO)-based therapeutics hold much promise for the treatment of neurodegenerative diseases. ASOs are chemically modified DNA oligomers that distribute widely throughout the CNS when dosed into the cerebral spinal fluid. They bind RNA and can be designed to halt or increase the production of proteins. SPINRAZA was recently approved by the FDA for the treatment of spinal muscular atrophy and we have several other antisense programs in clinical trials for Huntington's, Alzheimer's, and ALS. Here, we demonstrate that ASOs not only efficiently target neurons, but also oligodendrocytes (OLs), oligodendrocyte progenitor cells (OPCs), and astrocytes. First, using in situ hybridization (ISH), we find robust reduction of target RNA in white matter tracts throughout cynomolgus monkey CNS after an intrathecal injection of ASO targeting the non-coding RNA Malat1. Second, we show >90% reduction of target RNA in mouse CNS eight weeks after an intracerebroventricular (ICV) injection of ASO targeting OL-specific proteolipid protein 1 (Plp1), indicating that ASOs efficiently target OLs. Third, using double fluorescent ISH we demonstrate target RNA reduction in PDGFRa+ OPCs within lysolecithin lesions in the corpus callosum of mice dosed with Malat1 ASO. This indicates that OPCs are efficiently targeted by ASO in a demyelination context. Finally, we demonstrate near total reduction of transcript and protein in rodent astrocytes using

GFAP-targeted ASOs. Importantly, we have performed proof of concept studies in mouse and rat models of Alexander disease, a rare and fatal leukodystrophy driven by toxic accumulation of mutated GFAP, which forms Rosenthal fibers in astrocytes. GFAP-targeted ASOs markedly reduce target mRNA and protein in rodents, even within the context of the models' high overexpression. Within 2-4 weeks post-treatment, Rosenthal fibers degrade and the underweight animals gain weight and limb strength. These exciting results indicate that ASOs are a promising new platform for the treatment of Alexander disease and potentially additional myelin-related disorders such as other leukodystrophies, multiple sclerosis, traumatic injuries, and stroke.

Disclosures: B. Powers: A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ionis Pharmaceuticals. **T. Hagemann:** None. **C. Mazur:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ionis Pharmaceuticals. **F. Rigo:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ionis Pharmaceuticals. **A. Messing:** None. **E. Swayze:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ionis Pharmaceuticals.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.13/I7

Topic: B.11. Glial Mechanisms

Support: SICORP A*STAR-AMED

Title: The therapeutic potential of fingolimod against ischemia-induced suppression of oligodendrocyte differentiation

Authors: *K. YASUDA[1], T. MAKI[1], S. SAITO[3], Y. YAMAMOTO[3], H. KINOSHITA[1], K. NATSUE[2], M. IHARA[3], R. TAKAHASHI[1]
[1]Neurol., [2]Neurosurg., Kyoto Univ., Kyoto city, Japan; [3]Natl. Cerebral and Cardiovasc. Ctr., Suita, Japan

Abstract: [Background]Subcortical ischemic vascular dementia (SIVD) is the most common subtype of vascular dementia. SIVD is defined by evidence of subcortical white matter lesions in human. Injury of myelin/oligodendrocytes (OLGs) after chronic cerebral ischemia results in an abundant loss of myelin sheaths and axonal degeneration, which eventually lead to functional

disabilities. The failure to regenerate myelin due to impairment of oligodendrocyte precursor cell (OPC) differentiation is one of crucial pathomechanisms underlying ischemia-induced white matter damages. Therefore, the enhancement of OPC differentiation should be a promising therapeutic target for SIVD. Fingolimod, known as a drug used to treat multiple sclerosis, binds to the sphingosine 1-phosphate (S1P) receptor which is expressed not only on lymph nodes but also on neuronal, glial, and vascular cells in the brain, exerting various effects beside immunomodulation.[Object]The purpose of present study was to investigate whether fingolimod and related compounds exert positive effects on OPC function and regeneration under chronic ischemic condition.[Methods] For *in vitro* experiments, we prepared primary culture of OPCs and OLGs obtained from neonatal rats. To induce prolonged hypoxic conditions, OPCs were incubated with non-lethal concentration of $CoCl_2$ and were treated with or without fingolimod. Western blot analysis and immunocytochemistry were performed to examine the effect of fingolimod on OPC differentiation under ischemic condition. For *in vivo* experiments, we used a mouse model of prolonged cerebral hypoperfusion and white matter ischemic lesions generated by bilateral common carotid arteries stenosis (BCAS). Fingolimod was administered intraperitoneally to the BCAS-operated mice. On day 28 after surgery, mice were euthanized and western blot analysis and immunohistochemistry were performed.[Results]In vitro studies demonstrated that low concentration of fingolimod directly rescued ischemia-induced suppression of OPC differentiation via PI3K-Akt pathway, as shown by western blot and immunocytochemistry. Western blot analysis of *i*n vivo studies revealed that fingolimod treatment significantly ameliorated the decreased levels of myelin basic protein expression in the BCAS-operated mice. Immunohistochemistry showed that the number of newly generated mature OLGs in the corpus callosum was increased in fingolimod-treated mice on day 28 after BCAS.[Conclusion]The present study indicated that fingolimod can promote oligodendrogenesis under prolonged ischemic condition and the modulation of S1P signaling is a potential therapeutic target for SIVD.

Disclosures: K. Yasuda: None. **T. Maki:** None. **S. Saito:** None. **Y. Yamamoto:** None. **H. Kinoshita:** None. **K. Natsue:** None. **M. Ihara:** None. **R. Takahashi:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.14/I8

Topic: B.11. Glial Mechanisms

Support: NSFC (31771120, 81471346)
Chongqing Scientific and Technical Innovation Foundation of China (CSTCKJCXLJRC07)
Cheung Kong Scholars Program

NIH/NINDS (R01NS062796, R01NS097428, R01NS095889),
Adelson Medical Research Foundation (A130141)

Title: Enhancing oligodendrocyte myelination rescues synaptic loss and improves functional recovery after chronic hypoxia

Authors: F. WANG[1], J. Y. YANG[1], N. YANG[2], J. X. CHEN[2], S. P. FANCY[3], L. XIAO[2], J. R. CHAN[3], *F. MEI[1]
[1]Dept. of Histology and Embryology, [2]Dept. of Physiol., Third Military Med. Univ., Chongqing, China; [3]UCSF Weill Inst. for Neurosciences, Dept. of Neurology,, Univ. of California at San Francisco, San Francisco, CA

Abstract: White matter injury (WMI) in the brains of preterm infants leads to long-term functional neuronal impairment without any available clinical therapies. Although hypomyelination and arrested development of oligodendrocyte precursor cells (OPCs) are prominent in WMI, it is still unclear whether enhancing myelination represents a promising strategy to achieve functional recovery. As hypomyelination accompanies a number of pathological changes in WMI, determining the functional significance of myelination requires oligodendroglial-specific genetic manipulation. To address the significance of enhancing myelination for functional recovery after WMI, we characterized the hypomyelination deficit after chronic hypoxia, accompanied by structural and functional deficits of excitatory cortical synapses and a prolonged motor behavior deficit. To demonstrate the specific effect of hypomyelination on these features, we induced the oligodendroglial-specific deletion of the transcriptional factor Olig2, and demonstrate that a delay in myelination phenocopies the synaptic and functional deficits observed in adolescent mice after hypoxia, suggesting that functional developmental progression necessities proper spatiotemporal deposition of myelination. Additionally, these data suggest that myelin may even facilitate excitatory presynaptic innervation. As a gain of function, we induced oligodendroglial-specific deletion of the muscarinic receptor 1 (M1R), a negative regulator for oligodendroglial differentiation. The M1R deletion in OPCs enhances oligodendrocyte myelination and subsequently promotes the functional recovery and rescues the synaptic loss after chronic hypoxia. In line with this evidence, drug-based myelination-therapies also result in accelerated recovery of myelination and functional recovery after chronic hypoxia. Taken together, our data indicates that the loss of synapses and the functional deficits resulting from chronic hypoxia may be specifically and directly attributed to hypomyelination and that myelination-enhancing strategies represent a promising approach for functional recovery against WMI.

Disclosures: F. Wang: None. **J.Y. Yang:** None. **N. Yang:** None. **J.X. Chen:** None. **S.P. Fancy:** None. **L. Xiao:** None. **J.R. Chan:** None. **F. Mei:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.15/I9

Topic: B.11. Glial Mechanisms

Support: NIH award R25NS080685

Title: Glutathione antioxidant system is transiently upregulated in juvenile oligodendrocytes: Implications for development and ischemic response

Authors: *M. NEAL[1], D. VERDEN[2], W. B. MACKLIN[3]
[1]Cell and Developmental Biol. Dept., CU Anschutz, Aurora, CO; [2]UC Denver Anchutz Med. Campus, Aurora, CO; [3]Dept Cell & Dev Biol., Univ. Colorado Med. Sch., Aurora, CO

Abstract: Oligodendrocytes are the cells of the central nervous system (CNS) that wrap axons with myelin, which allows for the fast transduction of electrical signals. Oligodendrocytes rapidly produce myelin during development, entering a myelin maintenance stage once myelination is complete. The process of myelination generates reactive oxygen species (ROS) byproducts; however the mechanism by which myelinating oligodendrocytes mitigate oxidative stress is unknown. Because we have previously seen resistance to oxidative stress induced by ischemic/reperfusion (I/R) injury in juvenile oligodendrocytes, we are investigating the differences in antioxidant activity, specifically glutathione (GSH) metabolism, between juvenile and adult oligodendrocytes in both healthy and stroked tissue. GSH is a common antioxidant across many cell types that is known to be expressed at a low level in oligodendrocytes, but it may be required during active myelination to mitigate ROS by-products. Comparison of gene expression in oligodendrocytes acutely isolated from juvenile or adult striatum by qPCR revealed increased levels of GSH-regulating genes in juvenile oligodendrocytes relative to adult cells, along with an upregulation of GSH-related genes in response to I/R injury in juvenile oligodendrocytes. Furthermore, immunohistochemical (IHC) analysis of juvenile and adult striatum revealed increased expression of glutathione-synthesizing proteins, as well as maintenance of these proteins after stroke injury in juvenile oligodendrocytes. These results indicate that juvenile oligodendrocytes utilize the antioxidant GSH pathway during the process of active myelination, and that this pathway may provide for their protection from stroke injury.

Disclosures: D. Verden: None. **W.B. Macklin:** None.

Poster

649. Glia in Energy Homeostasis and Disease

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 649.16/I10

Topic: I.06. Computation, Modeling, and Simulation

Support: Synergy

Title: A reliable method for isolation and culture of different glial cells from adult pig brain

Authors: *G. K. TANTI[1], R. SRIVASTAVA[2], S. R. KALLURI[2], C. NOWAK[2], B. HEMMER[2,3]
[1]Dept. of Neurol., Tech. Univ. Munich, Munich, Germany; [2]Dept. of Neurol., Klinikum rechts der Isar, Tech. Univ. Munich, Munich, Germany; [3]Munich Cluster for Systems Neurol. (SyNergy), Munich, Germany

Abstract: Primary culture of glial cells is an important tool for basic and translational neuroscience research. Glial cell cultures are usually generated from rodent brain although considerable differences exist between human and rodent glia. Because many translational research projects aim to identify mechanisms that eventually lead to diagnostic and therapeutic approaches to target human diseases, glia cultures are needed that better reflect human glia. Pig brain is easily accessible and in many aspects close to the human brain. We have established an easy and cost-effective method to isolate and culture different primary glial cells from adult pig brain. Oligodendrocyte, astrocyte, and microglia primary cell cultures were generated from the same brain tissue and grown for 6-8 weeks. Primary oligodendrocyte cultures had a purity of 95%, showed the typical morphology and were O4, Olig2, MBP and MOG positive. Primary microglia cultures were 90% pure and expressed CD11b and Iba1. Astrocyte cultures showed the typical morphology with 60% of cells expressing GFAP. Human sera from patients with Neuromyelitis Optica containing AQP4 antibodies exerted a specific cytotoxic effect on astrocyte but not other glial cell cultures. In summary, we established a new method for primary oligodendrocyte, microglia and astrocyte cell cultures from the pig brain suitable for functional assays.

Disclosures: G.K. Tanti: None. **R. Srivastava:** None. **S.R. Kalluri:** None. **C. Nowak:** None. **B. Hemmer:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.01/I11

Topic: B.11. Glial Mechanisms

Support: Grant-in-Aid for Young Scientists (B) 16K18388

Title: Remodeling the brain after stroke by astrocytic phagocytosis via ABCA1-mediated pathway

Authors: *Y. MORIZAWA[1], S. KOIZUMI[2]
[1]Tohoku Univ., Sendai-Shi, Japan; [2]Dept. Neuropharmacol / Univ. Yamanashi, Yamanashi, Japan

Abstract: Remodeling the brain by clearance of unnecessary network and debris is thought to be essential for the maintenance of brain function and microenvironment. Emerging evidence has shown that not only microglia but astrocytes also contribute to the remodeling under pathological conditions via phagocytosis. Here, we show that astrocytes, other type of glia, also show highly phagocytic phenotype after stroke with different spatiotemporal patterns of microglia. Following transient brain ischemia, phagocytic astrocytes are observed within the ischemic penumbra region during the later stage of ischemia. However, phagocytic microglia are mainly observed within the ischemic core region during the earlier stage of ischemia. Phagocytic astrocytes upregulate ABCA1 and its pathway molecules, MEGF10 and GULP1, which are required for phagocytosis, and upregulation of ABCA1 alone is sufficient for enhancement of phagocytosis. Disrupting ABCA1 in reactive astrocytes result in fewer phagocytic inclusions after ischemia. Together, these findings suggest that astrocytes are transformed into a phagocytic phenotype as a result of increase in ABCA1 and its pathway molecules and contribute to recovery or remodeling of damaged tissues and penumbra networks.

Disclosures: Y. Morizawa: None. **S. Koizumi:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.02/DP02/I12

Topic: B.11. Glial Mechanisms

Title: AAV mediated trans-synaptic tagging of astrocytes: A novel tool for studying neuron-astrocyte interactions

Authors: *L. GEORGIOU, B. KUHN
Okinawa Inst. of Sci. and Technol. (OIST), Onna-son, Japan

Abstract: One of the most exciting modern hypothesis is that astrocytes respond to neuronal signals with calcium transients that in turn can influence neuronal activity. However, it is controversial whether astrocytes respond reliably to neuronal signals *in vivo.* Our objective was to develop a novel method to study neuron-astrocyte interactions *in vivo.* We show that recombinant adeno associated viruses (rAAVs) have trans-synaptic properties that can be exploited to reliably label axon-astrocyte pairs at high contrast and record their activity simultaneously *in vivo*. To confirm the trans-synaptic properties of rAAVs to astrocytes we used different combinations of vectors injected in the thalamus and cortex of adult (1-3-month-old), male and female mice (n > 100). rAAV injections labelled neurons densely at the injection site and sparsely astrocytes and neurons at the anterograde projection sites. Additionally, we find virus capsid proteins using immunohistochemistry in the labelled cells anterograde to the injection site. Now, we use this method combined with genetically encoded calcium indicators to study axon-astrocyte interactions with two-photon microscopy through a chronic cranial window in awake, head fixed mice. We show that astrocytes in the somatosensory cortex of awake mice exhibit fast calcium signals at the microdomains. We also show that astrocytes are in contact with thalamocortical axons. Exploratory correlation analysis of cortical astrocytes and contacting neurite calcium concentration recordings suggests that astrocytes do not respond to axon activity. We conclude that rAAVs have trans-synaptic properties and can infect both neurons and astrocytes anterogradely. This property of rAAVs can be used to study circuit specific axon-astrocyte interactions. Furthermore, the results challenge the spatial specificity of rAAVs and if cortical astrocytes reliably respond to neuronal activity *in-vivo.*

Disclosures: L. Georgiou: None. **B. Kuhn:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.03/I13

Topic: B.11. Glial Mechanisms

Title: Early upregulation of $K_V3.4$ expression and activity in reactive astrocytes of Alzheimer's disease Tg2576 mice

Authors: R. CICCONE[1], F. BOSCIA[1], I. PICCIALLI[1], A. CASAMASSA[1], A. VINCIGUERRA[1], *A. G. SADILE[2], G. DI RENZO[1], L. ANNUNZIATO[1], A.

PANNACCIONE[1]
[1]Dept. of Neuroscience, Reproductive and Odontostomatological Sci., FEDERICO II Univ. of Naples, 80131, Napoli, Italy; [2]Exptl. Med. Dept., Univ. of Campania Luigi Vanvitelli, Napoli, Italy

Abstract: Astrocyte dysfunction emerges early in Alzheimer's disease (AD) and may contribute to its pathology and progression (Verkhratsky et al. 2011; Zhao et al. 2011; Couturier et al. 2016). Recently, the voltage gated potassium channel $K_V3.4$ subunit, which underlies the fast-inactivating K^+ currents, has been recognized to be relevant for AD pathogenesis and is emerging as a new target candidate for AD (Angulo et al. 2004; Pannaccione et al. 2007). In the present study, we investigated both in in vitro and in vivo models of AD the expression and functional activity of $K_V3.4$ potassium channel subunits in astrocytes. In primary astrocytes biochemical, immunohistochemical, and electrophysiological studies demonstrated a time-dependent upregulation of $K_V3.4$ expression and functional activity after exposure to amyloid-β (Aβ) oligomers. Consistently, astrocytic $K_V3.4$ expression was upregulated in the cerebral cortex, hippocampus, and cerebellum of 6-month-old Tg2576 mice. Further, confocal triple labeling studies revealed that in 6-month-old Tg2576 mice, $K_V3.4$ was intensely coexpressed with Aβ in nonplaque associated astrocytes. Interestingly, in the cortical and hippocampal regions of 12-month-old Tg2576 mice, plaque-associated astrocytes much more intensely expressed $K_V3.4$ subunits, but not Aβ. More important, we evidenced that the selective knockdown of $K_V3.4$ expression significantly downregulated both glial fibrillary acidic protein levels and Aβ trimers in the brain of 6-month-old Tg2576 mice. Collectively, our results demonstrate that the expression and function of $K_V3.4$ channel subunits are precociously upregulated in cultured astrocytes exposed to Aβ oligomers and in reactive astrocytes of AD Tg2576 mice.

Disclosures: R. Ciccone: None. **F. Boscia:** None. **I. Piccialli:** None. **A. Casamassa:** None. **A. Vinciguerra:** None. **A.G. Sadile:** None. **G. Di Renzo:** None. **L. Annunziato:** None. **A. Pannaccione:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.04/I14

Topic: B.11. Glial Mechanisms

Support: Dorothy Goodwin Women's Initiative at the University of Hartford

Title: The effect of γ-synuclein treatment on adult human cortical astrocyte proliferation and BDNF expression

Authors: T. LE[1], C. L. WINHAM[1], E. C. WILKIE[1], E. R. JELLISON[2], *A. O. KOOB[1]
[1]Neurosci. Program, Univ. of Hartford, West Hartford, CT; [2]Immunol., Univ. of Connecticut Hlth. Ctr., Farmington, CT

Abstract: γ-Synunclein (γ-syn), a member of the synuclein protein family implicated in neurodegenerative disease, is expressed by astrocytes in the human nervous system, and increased extracellularly in the cerebrospinal fluid of individuals diagnosed with Alzheimer's disease and Dementia with Lewy Bodies. Upregulation of γ-syn has also been shown in glioblastomas and other cancers. In order to better understand the function of extracellular γ-syn, astrocytes from adult human cortex in tissue culture were treated with 100 nM γ-syn for 3, 6 and 24 hours. Western blot analysis revealed endogenous expression of γ-syn in controls as well as uptake of extracellular γ-syn by astrocytes at 3 and 6 hours, with a further increase at 24 hours. Brain derived neurotophic factor (BDNF), a growth factor released by astrocytes, was increased intracellularly over time with γ-syn treatment, but not in controls, and coincided with elevated extracellular BDNF release at 6 hours. However, after 24 hours of treatment, extracellular BDNF was decreased after γ-syn treatment compared to controls. Astrocytes labeling with proliferation marker 5-bromodeoxyuridine (BrdU) were increased at 3 hours as well as 6 hours after γ-syn treatment, but not at 24 hours. Additionally, after cell synchronization in G_0/G_1, cells were released back into the cell cycle and treated with BrdU and 50, 100 and 150 nM of γ-syn for 24 and 48 hours. Analysis of BrdU and propidium iodide through flow cytometry 24 hours after release revealed an increase in G_2/M phase of the cell cycle in cells treated with 100 nM γ-syn compared to controls. This effect was no longer seen at 48 hours. However, BDNF release was increased after 100 nM and 150 nM γ-syn treatment at 48 hours, with no difference from controls after 24 hours. These results suggest γ-syn treatment initially causes upregulation of the cell cycle and subsequent BDNF release in human cortical astrocytes. Since stimulation of reentry into the cell cycle by non-neuronal cells is shown in neurodegenerative disease, dysregulation of endogenous γ-syn in the aging brain could potentially contribute to this process.

Disclosures: T. Le: None. **C.L. Winham:** None. **E.C. Wilkie:** None. **E.R. Jellison:** None. **A.O. Koob:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.06/I16

Topic: B.11. Glial Mechanisms

Title: Direct effects of polychlorinated biphenyls and synuclein on astrocyte function

Authors: *M. S. MCCANN[1], K. MAGUIRE-ZEISS[2]
[1]Georgetown Univ., Washington, DC; [2]Neurosci. & IPN, Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Synucleinopathies are diseases characterized by the accumulation of oligomeric α-synuclein (syn) where the central nervous system (CNS) is the primary organ system affected. While the etiology of synucleinopathies remains elusive, evidence suggests that the intersection of environmental stressors and genetic predispositions result in neurodegeneration. The accumulation of polychlorinated biphenyls (PCBs), a class of hazardous organic chlorines once widely used for industrial purposes, is correlated with increased nigral cell death in Parkinson's disease (PD) patients. Astrocytes have a critical role in maintaining brain homeostasis and do so through their robust antioxidant profiles. Here, we hypothesize that syn and PCB act as a 'dual hit' in inciting disease pathogenesis, for which astrocyte dysfunction is a critical component. We found that PCBs and syn individually cause significant lipid peroxidation and increased expression of specific Nrf2 antioxidant genes in primary murine astrocytes. To investigate whether these compounds serve as a 'dual hit' in inciting astrocytic dysfunction, we co-treated astrocytes with PCBs and syn and found significant astrocytic release of monocyte chemoattractant protein-1 (MCP-1). Overall, this study suggests that syn and PCBs have a synergistic effect *in vitro*, and future work will use an *in vivo* dual hit model.

Disclosures: M.S. McCann: None. **K. Maguire-Zeiss:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.07/I17

Topic: B.11. Glial Mechanisms

Support: National Institute on Aging: 1K01AG042500
Delaware IDeA Network of Biomedical Research Excellence (INBRE) Pilot Award: NIH-NIGMS: 5P20GM103446
NIH-NIGMS Centers of Biomedical Research Excellence (COBRE): 5P20GM103653
National Science Foundation (MRI): 1728804
Delaware Economic Development Office Grant from the State of Delaware

Title: Astrocyte specific expression of TDP-43 alters memory and anxiety

Authors: *C. M. KHALID-JANNEY, S. DAVIS, D. CARTER, M. A. GITCHO
Biol. Sci., Delaware State Univ., Dover, DE

Abstract: TAR DNA binding protein 43 (TDP-43) functions as a heterogeneous nuclear ribonucleoprotein that regulates gene expression, RNA stability, and localizes to the cytoplasm as a stress response protein. Glial Fibrillary Acidic Protein (GFAP) is an intermediate filament protein found primarily in astrocytes that increases expression when astrocytes are activated. TDP-43 predominantly resides in the nucleus except under pathological conditions it accumulates in the cytoplasm. In this study, we selectively and conditionally express TDP-43 with a defective nuclear localization signal (ΔNLS) under control of the human GFAP promoter in astrocytes utilizing a doxycycline inducible system to investigate pathological outcomes and non-cell autonomous effects associated with TDP-43 expression. We hypothesize that age-dependent selective TDP-43ΔNLS expression in astrocytes alters memory and anxiety through in a mechanism of non-cell autonomous neuronal degeneration.
At two months of age, GFAP/TDP-43ΔNLS mice displayed functional changes in anxiety and memory, which may be associated with the changes in non-cell autonomous neuronal degeneration. In addition, primary cortical neuron/astrocyte co-cultures expressing TDP-43ΔNLS exclusively in astrocytes showed a significant decrease in neuronal viability compared with littermate controls.
Mice were tested via a battery of behavioral tests across multiple time points (8/12/16 weeks), consisting of anxiety tests (Light/Dark Box, Open Field, Hole Board, Elevated Plus Maze), memory tests (8-Arm Radial Maze (ARM), Y Maze), motor tests (Rotarod, Elevated Beam), and a sociability test (3-Box/Resident Intruder), in differing combinations at each time point. Additionally, primary cortical neuron/astrocyte (~90%/~10%) cultures comparing GFAP and GFAP/TDP-43ΔNLS mice were examined for viability, immunofluorescence, Western blot, and mitochondrial bioenergetics. Pathology and biochemistry in the brain and was also evaluated at the three behavioral time points (8/12/16 weeks). This relationship of non-cell autonomous degeneration may expand our knowledge of astrocyte dysfunction associated with neurodegeneration.

Disclosures: C.M. Khalid-Janney: None. **S. Davis:** None. **D. Carter:** None. **M.A. Gitcho:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.08/J1

Topic: B.11. Glial Mechanisms

Support: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
Ministério da Saúde
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)

Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ)

Title: Astrocytes are target of a-synuclein oligomers: Implications for astrocyte reactivity and synapse formation in Parkinson's disease model

Authors: *L. P. DINIZ[1], I. MATIAS[2], M. GARCIA[2], A. P. B. ARAUJO[2], S. V. ALVES-LEON[2], J. M. SOUZA[2], D. FOGUEL[2], C. P. FIGUEIREDO[2], C. BRAGA[2], L. F. ROMÃO[2], F. C. A. GOMES[2]
[1]Inst. of Biomed. Sci., Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [2]Federal Univ. of Rio de Janeiro,, Rio de Janeiro, Brazil

Abstract: Parkinson's disease (PD) is characterized by selective death of dopaminergic neurons in the substantia nigra, alterations in the basal ganglia circuit, increase of glutamatergic synapses in the striatum and aggregation of α-Synuclein. Evidence suggest that oligomeric species of α-Synuclein (αSO) are the genuine neurotoxins of PD. Whereas several studies support the direct neurotoxic effects of αSO on neurons, their effects on astrocytes have never been directly addressed. Astrocytes are essential to synapse formation and function, including maintenance of neurotransmitters levels in the synaptic cleft in homeostatic condition. However, the role of reactive astrocytes in synaptic regulation in neurodegenerative diseases is unclear. Here, we evaluated the effects of αSO on astrocyte reactivity and regulation of striatal glutamatergic synapses. We showed that αSO increases the expression of complement component 3 (C3), the proinflammatory cytokines tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6), in addition to regulate the nitric oxide levels in astrocyte cultures. Additionally, we observed that αSO enhanced the synaptogenic capacity of astrocytes by increasing the levels of the known synaptogenic molecule, transforming growth factor beta 1 (TGF-β1). Moreover, intracerebroventricular injection of αSO in mice increased the number of astrocytes, the density of excitatory synapses, as well as TGF-β1 levels in the caudate-putamen of injected animals. Inhibition of TGF-β1 signaling impaired the synaptogenesis effect of the astrocyte conditioned medium on glutamatergic synapses *in vitro;* whereas addition of purified TGF-β1 protected dopaminergic neurons against synapse loss triggered by αSO. Together, our data suggest that αSO have important effects on astrocytic functions, and describe TGF-β1 as a new endogenous astrocyte-derived molecule involved in the increase of striatal glutamatergic synaptic density present in early stages of PD.

Disclosures: I. Matias: None. **M. Garcia:** None. **A.P.B. Araujo:** None. **S.V. Alves-Leon:** None. **J.M. Souza:** None. **D. Foguel:** None. **C.P. Figueiredo:** None. **C. Braga:** None. **L.F. Romão:** None. **F.C.A. Gomes:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.09/J2

Topic: B.11. Glial Mechanisms

Support: Fondecyt Postdoctoral #3170645

Title: Differential gene expression in reactive mouse astrocytes and astrocytes from the $SOD1^{G93A}$ mutated ALS model

Authors: *R. D. PÉREZ, L. LEYTON
ICBM, Fac. Medicine,University of Chile, Santiago, Chile

Abstract: When activated by brain damage (e.g. Amyotrophic Lateral Sclerosis, ALS), astrocytes undergo hypertrophy, proliferate and migrate to the damaged zone. Altogether, this process is known as “reactive gliosis” or "astrogliosis", and although required to protect the brain, astrogliosis represents a major obstruction to nerve regeneration. Such lack of repair is due to the presence of inhibitory molecules, including proteins secreted by these reactive astrocytes. In addition, reactive astrocytes undergo changes at the subcellular level and rearrange the expression and localization of cell surface proteins; however, changes in gene expression levels of signaling pathways involved in astrogliosis remain unclear. We analyzed using bioinformatics approaches different datasets (GSEs) to explore and identify changes in the expression of molecules from reactive astrocytes as compared to astrocytes from the normal rat brain and primary astrocytes obtained from the ALS mouse model (animals with $SOD1^{G93A}$ mutated). *In silico* analysis was validated using primary cultures of astrocytes, and from the ALS mice, to test levels of expression of the most relevant genes by western blotting. The bioinformatic analysis revealed that signaling pathways such as regulation of actin cytoskeleton and focal adhesion were those that showed most significant alterations in gene expression in reactive and ALS astrocytes compared with normal astrocytes. β3-integrin, a cell adhesion molecule important in cytoskeleton regulation and focal adhesion formation, as well as the glial fibrillary acidic protein (a marker of astrocyte reactivity), were found to be elevated in reactive astrocytes and ALS-derived astrocytes compared to their respective controls. Bioinformatics analysis provided us with relevant information regarding genes involved in crucial signaling pathways that are altered in astrogliosis. Importantly, expression of some identical genes was similarly affected in the ALS condition.

Disclosures: R.D. Pérez: None. **L. Leyton:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.10/J3

Topic: B.11. Glial Mechanisms

Support: Synapsis Foundation – Alzheimer Research Switzerland ARS

Title: Using mild uncoupling in mitochondria of astrocytes to rescue spatial memory in Alzheimer's disease

Authors: *N. ROSENBERG[1], A.-B. ROCHER[1], L. RESTIVO[1], Y. BERNARDINELLI[2], M. BRIQUET[1], J.-Y. CHATTON[1]
[1]Univ. of Lausanne, Lausanne, Switzerland; [2]Neonomia, Geneva, Switzerland

Abstract: Oxidative stress has been associated with apoptosis and cell death in neurodegenerative diseases such as Alzheimer's disease (AD). It has been shown *in vitro* that mitochondrial uncoupling proteins (UCPs) endogenously expressed by astrocytes decrease peroxide production from astrocytes, increase glycolysis and lactate release, and enhance survival rate of neurons. Lactate exerts beneficial effects in cerebral ischemia and has a non-metabolic modulatory effect on neuronal activity. Furthermore, in neurons, lactate is involved in the potentiation of NMDA receptors that are key players in synaptic plasticity and in long-term memory consolidation. We therefore hypothesize that overexpression of astrocytic UCP4 *in vivo* will provide support to neurons facing AD-associated injuries. Adeno-associated virus (AAV) containing UCP4 alone, or UCP4 in combination with mCherry as a fluorescent reporter under the GFAP promoter were stereotaxically injected in the CA1-CA3 of the dorsal hippocampus of wild-type (WT) and 3xTg-AD (3xTg) mice. We assessed the cognitive status in a first set of 3 month-old and 7 month-old mice. The viral construct designed had no effect on the exploratory behavior in both groups. While 3 month-old WT mice react to the spatial change, 3xTg mice fail to selectively explore the displaced object. Overall, uncoupling mitochondria of astrocyte appear to rescue spatial memory deficits. Whether this effect is due to long term mitochondrial uncoupling has to be confirmed. In parallel, we are assessing the electrophysiological properties of CA1 pyramidal cell of the same animals, by using the patch-clamp technique. Further experiments will allow us to tackle the question of whether astrocytic UCP4 influences lactate and ROS production *in vivo* and alters the function and health of vulnerable neurons of AD-associated pathologies.

Disclosures: N. Rosenberg: None. **A. Rocher:** None. **L. Restivo:** None. **Y. Bernardinelli:** None. **M. Briquet:** None. **J. Chatton:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.11/J4

Topic: B.11. Glial Mechanisms

Support: GACR 16-10214S
GAUK 636316
CZ.2.16/3.1.00/21527

Title: Age-related changes in astrocyte swelling and their volume regulation

Authors: *M. ANDEROVA[1,2], D. KOLENICOVA[1], D. KIRDAJOVA[1], L. VALIHRACH[3], J. TURECKOVA[1], J. KRISKA[1], A. SULAKOVA[1], B. ELIASOVA[1], M. KUBISTA[3]
[1]Inst. Exper Med. ASCR, Prague 4, Czech Republic; [2]Dept of Neurosci., Second Fac. of Medicine, Charles Univ. in Prague,, Prague, Czech Republic; [3]Lab. of Gene Expression,, Inst. of Biotechnology, Acad. of Sci. of the Czech Republic, Vestec, Czech Republic

Abstract: Astrocytes are multifunctional cells, which play essential roles in the brain development, physiology and pathology. The age-related morphological changes and loss of normal astrocyte functions may contribute to the onset and progression of various neurodegenerative pathologies and dementia.
Here, we have focused on age-related changes in astrocyte functioning, predominantly on astrocyte ability to regulate their volume in response to pathological stimuli. The volume changes of hippocampal astrocytes were quantified using three-dimensional confocal morphometry in acute brain slices isolated from 3M, 9M, 12M and 18M old GFAP/EGFP mice. The slices were exposed either to 20-minute hypoosmotic stress or to severe hyperkalemia (50mM K+). Under the exposure to hypotonic solutions the astrocyte swelling was maximal in 3M old mice, where the volume increased by 30%, and the extent of their swelling continually decreased during aging. Interestingly, the exposure to high K+ concentration evoked similar swelling in 3M and 12M old animals (by 65-70%), while in 9M and 18M old animals the swelling was markedly smaller (by 35-40%).
In addition, a single cell RT-qPCR profiling was carried out to reveal possible differences in the expression levels of ion channels/transporters that participate in maintaining ionic and neurotransmitter homeostasis and contribute to the astrocyte swelling and their volume regulation. Based on the Self-organizing map analysis, a single cell RT-qPCR revealed the presence of three astrocytic subpopulations, of which incidence significantly differed during aging.
Supported by: GACR 16-10214S from the Grant Agency of the Czech Republic and GAUK 636316 from the Grant Agency of Charles University and project "Advanced Bioimaging of

Living Tissues",reg.n.CZ.2.16./3.1.00/21527, which was financed from the budget of the European Regional Development Fund and public budgets of the Czech Republic through the Operational Programme Prague-Competitiveness.

Disclosures: M. Anderova: None. **D. Kolenicova:** None. **D. Kirdajova:** None. **L. Valihrach:** None. **J. Tureckova:** None. **J. Kriska:** None. **A. Sulakova:** None. **B. Eliasova:** None. **M. Kubista:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.12/J5

Topic: B.11. Glial Mechanisms

Support: NIH Grant AG048814
Glenn Foundation Grant
Esther B. O'Keeffe Charitable Foundation
JPB Foundation
European Molecular Biology Organization Fellowship
Merck Research Laboratories postdoctoral fellowship (administered by the Life Science Research Foundation)

Title: Normal aging induces A1-like astrocyte reactivity

Authors: *L. CLARKE[1], S. A. LIDDELOW[2], C. CHAKRABORTY[1], A. E. MUNCH[1], M. HEIMAN[3], B. A. BARRES[1]
[1]Neurobio., Stanford Univ., Stanford, CA; [2]Alexandria Ctr. for Life Sci., NYU Neurosci. Inst., New York, NY; [3]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: The decline of cognitive function occurs with aging, but the mechanisms responsible are unknown. Astrocytes instruct the formation, maturation, and elimination of synapses, and impairment of these functions has been implicated in many diseases. These findings raise the question of whether astrocyte dysfunction could contribute to cognitive decline in aging. We used the Bac-Trap method to perform RNA sequencing of astrocytes from different brain regions across the lifespan of the mouse. We found that astrocytes have region-specific transcriptional identities that change with age in a region-dependent manner. We validated our findings using fluorescence in situ hybridization and quantitative PCR. Detailed analysis of the differentially expressed genes in aging revealed that aged astrocytes take on a reactive phenotype of neuroinflammatory A1-like reactive astrocytes. Hippocampal and striatal astrocytes up-regulated a greater number of reactive astrocyte genes compared with cortical astrocytes. Moreover, aged brains formed many more A1 reactive astrocytes in response to the neuroinflammation inducer

lipopolysaccharide. We found that the aging-induced up-regulation of reactive astrocyte genes was significantly reduced in mice lacking the microglial-secreted cytokines (IL-1α, TNF, and C1q) known to induce A1 reactive astrocyte formation, indicating that microglia promote astrocyte activation in aging. Since A1 reactive astrocytes lose the ability to carry out their normal functions, produce complement components, and release a toxic factor which kills neurons and oligodendrocytes, the aging-induced up-regulation of reactive genes by astrocytes could contribute to the cognitive decline in vulnerable brain regions in normal aging and contribute to the greater vulnerability of the aged brain to injury.

Disclosures: L. Clarke: None. **S.A. Liddelow:** None. **C. Chakraborty:** None. **A.E. Munch:** None. **M. Heiman:** None. **B.A. Barres:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.13/DP03/J6

Topic: B.11. Glial Mechanisms

Support: NIH R01 AG054598

Title: *In vivo* multiphoton astrocytic imaging in the APPswe/PS1dE9 mouse model of Alzheimer's disease

Authors: *P. KELLY, S. S. HOU, M. CALVO RODRIGUEZ, S. J. VAN VELUW, B. J. BACSKAI
Mgh/Harvard Med. Sch., Boston, MA

Abstract: While synaptic dysfunction is a strong pathological correlate of memory dysfunction in Alzheimer's disease (AD), the causative mechanisms are unknown which limits the clinical management of individuals living with AD. Astrocytes critically support synaptic structure and function but undergo a series of complex morphological and functional alterations in AD. Our working hypothesis is that the astrocytic alteration in AD contributes to neurodegeneration and is a potential therapeutic target. Aged wild-type and APPswe/PS1dE9 (APP/PS1) transgenic mice each received a 3 μL bihemispheric intracortical injection of the ratiometric genetically encoded calcium indicator, Yellow Cameleon 3.6 (YC3.6) under the regulation of GFA2 promoter followed by the surgical removal of a 6-8 mm circular skull portion above the somatosensory cortex. Animals were provided with post-operative care and given at least 21 days to recover from surgery prior to being habituated to awake multiphoton *in vivo* imaging at 12 months of age. The astrocyte specific expression of fluorescent proteins resulted in the full delineation of astrocytes throughout hundreds of microns of intact murine cortex at high resolution. The intracellular astrocytic calcium transients in awake animals were heterogeneous and occurred

with less frequency within the soma when compared to the proximal, perisynaptic and perivascular processes. There was a trend towards increased baseline calcium levels within the astrocytes of awake 12-month old APP/PS1 mice when compared to age-matched wild-type animals. These preliminary data are in agreement with earlier findings from our laboratory that revealed a global elevation in astrocytic calcium activity within anesthetized 6-8 month old APP/PS1 mice when compared to age-matched wild-type mice and collectively implicate the role of aberrant astrocytic calcium homeostasis in the neurodegeneration in AD.

Disclosures: P. Kelly: None. **S.S. Hou:** None. **M. Calvo Rodriguez:** None. **S.J. Van Veluw:** None. **B.J. Bacskai:** None.

Poster

650. Glial Mechanisms in Neurodegenerative Diseases

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 650.14/J7

Topic: B.11. Glial Mechanisms

Support: NIH P30:GM122733

Title: Role of insulin-like growth factor 1 in astrocytic regulation of learning and memory in aging

Authors: *D. PRABHU[1], J. MARSHALL[1], K. BLACKBURN[1], N. M. ASHPOLE[2]
[1]Univ. of Mississippi, Oxford, MS; [2]Univ. of Mississippi, University, MS

Abstract: Advancements in healthcare have increased the average life span of people all over the world, thereby making them susceptible to disorders of aging. Aging of the brain is associated with a decline in learning, memory and cognition, affecting the ability to lead an independent life and posing an enormous economic burden. However, we still do not have an effective therapy for treating cognitive impairment. Insulin-like Growth Factor (IGF)-1, known to promote learning and memory, decreases with age. Majority of the studies have focused on the effects of IGF-1 on neurons, and not on astrocytes, despite the fact that it is the astrocytes that are the predominant cell type in the brain. One of the key functions of astrocytes is regulation of the glutamate-glutamine cycle. IGF-1 is known to influence some of the key proteins involved in this cycle. This project aims at investigating the effects of IGF-1 on the ability of astrocytes to release and recycle signaling molecules that transmit messages to nearby neurons as well as astrocytes.
We have measured the amount of glutamate released by cultured rat astrocytes under basal and stimulated conditions, in response to exogenous IGF-1 or PPP- which is an antagonist of IGF-1, with short-term and long-term treatments, using the Amplex red glutamate assay. Additionally, we have measured the changes in gene and protein expression of several key transporters

associated with the transport of glutamate in astrocytes, with qPCR and Western blotting respectively. Furthermore, we will look at the amounts of ATP released in response to IGF-1 and PPP, under basal and stimulated conditions, using a luminescence ATP measurement assay kit. Our results indicate that IGF-1 is critical for glutamate handling by astrocytes. We have observed that the amount of glutamate released into the media by astrocytes increases when treated with an inhibitor of IGF-1. We are currently measuring the gene and protein expression levels of key glutamate transporters.
In the future we plan to examine the same endpoints after genetic ablation of IGF-1 receptor using Cre-Lox recombination technology. Overall, this project will help uncover the role of IGF-1 in astrocytic regulation of learning and memory.

Disclosures: D. Prabhu: None. **J. Marshall:** None. **K. Blackburn:** None. **N.M. Ashpole:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.01/J8

Topic: B.11. Glial Mechanisms

Support: NSFC 81790642
NSFC 31671078

Title: EphrinB/EphB forward signaling in Müller cells causes apoptosis of retinal ganglion cells by increasing tumor necrosis factor alpha production in rat experimental glaucomatous model

Authors: *Z. WANG, S.-T. LIU, S.-M. ZHONG, X.-Y. LI, F. GAO, F. LI, M.-L. ZHANG, Y. MIAO, X.-L. YANG
Fudan Univ., Shanghai, China

Abstract: It was previously shown that EphB/ephrinB reverse signaling in retinal ganglion cells (RGCs) is activated and involved in RGC apoptosis in a rat chronic ocular hypertension (COH) model. In the present study, effects of ephrinB/EphB forward signaling in Müller cells were explored in the rat COH model. Treatment of cultured Müller cells with ephrinB1-Fc, an EphB1 activator, or intravitreal injection of ephrinB1-Fc in normal rats induced an increase in phosphorylated EphB levels in these cells, indicating the activation of ephrinB/EphB forward signaling, similar to that in COH retinas. The above treatment did not induce Müller cell gliosis, as evidenced by unchanged GFAP expression, but significantly up-regulated mRNA and protein levels of tumor necrosis factor-α (TNF-α) in Müller cells, thereby promoting RGC apoptosis. Production of TNF-α induced by the activation of ephrinB/EphB forward signaling was mediated by the NR2B subunit of NMDA receptors, which was followed by a distinct PI3K/Akt/NF-κB

signaling pathway, as pharmacological interference of each step of this pathway caused a reduction of TNF-α production, thus attenuating RGC apoptosis. Functional analysis of forward and reverse signaling in such a unique system, in which ephrin and Eph exist respectively in a glial element and a neuronal element, is of theoretical importance. Moreover, our results also raise a possibility that suppression of ephrinB/EphB forward signaling may be a new strategy for ameliorating RGC apoptosis in glaucoma.

Disclosures: Z. Wang: None. **S. Liu:** None. **S. Zhong:** None. **X. Li:** None. **F. Gao:** None. **F. Li:** None. **M. Zhang:** None. **Y. Miao:** None. **X. Yang:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.02/J9

Topic: B.11. Glial Mechanisms

Support: CONACYT 255087
Conacyt

Title: GLAST regulates its own mRNA levels

Authors: D. HERNÁNDEZ-MELCHOR[1], M. ESCALANTE[2], L. CID[2], *E. LOPEZ-BAYGHEN[3], A. ORTEGA[2]
[1]Toxicology, Cinvestav-IPN, Toxicology, Mexico City, Mexico; [2]Toxicology, Cinvestav-IPN, Toxicology, Ciudad de Mexico, Mexico; [3]Toxicology, Cinvestav-IPN, Dept. De Toxicología, Ciudad DE Mexico, Mexico

Abstract: Glutamate removal from synaptic cleft is carried out by transporter systems such as GLAST, a high affinity Na^+-dependent glutamate/aspartate transporter. GLAST regulation is under transcriptional glutamate-dependent control through PKC. The time-dependent reduction of H^3-labeled D-Aspartate (D-Asp) uptake and lack of effect when selective glutamate receptor agonists were used prompted us to explore the plausible transcriptional self-regulation of GLAST using the established model of cultured cerebellar Bergmann glia cells (BGCs) which present a predominant expression of GLAST. *chglast* is down-regulated in a dose- and time-dependent manner when BGCs were exposed to D-Aspartate (D-Asp). A 50 % decrease in GLAST mRNA was detected after 12 h of 150 µM D-Asp stimuli, this effect continues until 24 h of treatment. Similarly, 24 h exposure to 150 and 1000 µM of D-Asp diminished *chglast* in about 50%. In every condition cellular viability was unaltered. Interestingly, D-Asp enhances in 20% the effect of the transportable glutamate inhibitor PDC (trans-4-Carboxy-L-proline) over *glast*, reducing its expression to 50 %. Moreover, D-Asp reverts the effect of TBOA (DL-threo-β-Benzyloxyaspartic acid), a selective non-transportable inhibitor of EAATs, and diminishing

chglast expression to 70 % when compared to an untreated control. The use of D-Asp instead of glutamate guarantees that the observed effects are no related to receptor activation, but to the transporter itself. This results suggest that GLAST self-regulation is under transcriptional control via PCK.

Disclosures: D. Hernández-Melchor: None. **M. Escalante:** None. **L. Cid:** None. **E. Lopez-Bayghen:** None. **A. Ortega:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.03/J10

Topic: B.11. Glial Mechanisms

Support: 17H03988
17H05738

Title: Real-time imaging of activity-driven synapse-microglia interaction *in vitro*

Authors: *M. ANDOH, R. KOYAMA, Y. IKEGAYA
Grad Sch. Pharma Sci, Univ. Tokyo, Tokyo, Japan

Abstract: Synaptic remodeling is fundamental for the refinement of neural circuits. Accumulating evidences have suggested that the brain-resident immune cells microglia are executors of synaptic remodeling. Microglia tend to engulf less active synapses during development, while activity-dependent microglial touch to spines has been shown to result in spine growth in adulthood. However, it remains unclear how microglia detect the difference of neuronal activity and modulate synapses. To answer the question, we established a live imaging system of microglia-synapse interactions *in vitro* in which neuronal activity can be modulated. We cultured neurons with both microglia and astrocytes, which allowed microglia to exhibit ramified morphology. For performing real-time imaging, glial cocultures were prepared from $CX3CR1^{GFP/+}$ mice whose microglia express GFP and neurons were transfected with synaptophysin-RFP. Using this coculture system, we successfully captured an actual moment of synaptic pruning by microglia and are now investigating whether neuronal activity affects synaptic remodeling by microglia, using the DREADD system.

Disclosures: M. Andoh: None. **R. Koyama:** None. **Y. Ikegaya:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.04/J11

Topic: B.11. Glial Mechanisms

Support: NIH Grant EYO19277
NIH Grant F31NS086241
NIH Grant F31NS105249
NIH Grant T32NS007489

Title: Noradrenergic modulation of microglial dynamics and synaptic plasticity

Authors: *R. STOWELL[1], G. O. SIPE[2], A. K. MAJEWSKA[3]
[1]Univ. of Rochester, Rochester, NY; [2]MIT, Cambridge, MA; [3]Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Microglia, the innate immune cells of the central nervous system (CNS), respond rapidly and dynamically to homeostatic perturbations of the CNS milieu. In the healthy unperturbed brain, microglial processes make frequent contacts with neurons at synapses, impacting synaptic remodeling and turnover of dendritic spines. However, it remains unclear what receptors and signaling pathways govern microglial surveillance and synapse monitoring. Noradrenaline is a powerful signal that can affect many aspects of synaptic function and plasticity. Because microglia express high levels of β_2 adrenergic receptors (ARs) compared to other cell types in the brain, we asked whether noradrenergic tone could alter microglial behavior with respect to synapses through β_2 AR signaling. To test this hypothesis we have manipulated β_2 AR signaling pharmacologically using the following agents: Nadolol (blood brain barrier (BBB) impermeant β AR antagonist), Clenbuterol (BBB permeant β_2 AR agonist), and ICI 118-551 (BBB permeant β_2 AR antagonist). We paired nadolol with clenbuterol to stimulate β_2 ARs centrally without concomitant peripheral stimulation. We then evaluated changes in basic microglial physiology through a combination of *in vivo* two-photon microscopy and immunohistochemical staining for Iba-1, a microglia-specific protein. We have found that stimulation of β_2 AR signaling *in vivo* reduces microglial motility and pseudopodia formation and causes microglia to assume a less ramified morphology. We also found that stimulation of β_2 ARs leads to impaired microglial responsiveness to focal tissue injury. These experiments show that β_2 AR signaling can affect microglial physiology and immune responses. We next examined whether these changes in basic microglial function could impact microglial interactions with neurons and functional experience-dependent plasticity. Using intrinsic optical signal imaging we have shown that pharmacological manipulation of β_2 AR signaling impairs ocular dominance plasticity in the visual cortex during the visual critical period in mice. We have shown that

microglia are directly involved in this impairment through cre-mediated excision of β_2 AR specifically in microglia, which eliminates the effect of AR signaling on plasticity. Based on our results we believe that β_2 AR signaling serves important roles in modulating microglial physiology in the context of synaptic refinement. These results and future findings will improve our understanding of the signaling mechanisms that govern microglial interactions with synapses and how they impact activity-dependent synaptic modifications.

Disclosures: R. Stowell: None. **G.O. Sipe:** None. **A.K. Majewska:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.05/J12

Topic: B.11. Glial Mechanisms

Support: JSPS KAKENHI Grant 18H02756
JSPS KAKENHI Grant 18K15534
JSPS KAKENHI Grant 18K07620
GSK Japan Research Grant 2016

Title: Cellular localization of lysophosphatidic acid receptor 1 in the mouse brain

Authors: *N. KAJITANI[1], M. OKADA-TSUCHIOKA[1], H. ABE[1], W. OMORI[1,2], K. ITAGAKI[1,2], M. TAKEBAYASHI[1,2,3]
[1]Div. of Psychiatry and Neuroscience, Inst. for Clin. Res., [2]Dept. of Psychiatry, NHO Kure Med. Ctr. and Chugoku Cancer Ctr., Hiroshima, Japan; [3]Dept. of Neuropsychiatry, Fac. of Life Sciences, Kumamoto Univ., Kumamoto, Japan

Abstract: [Background] Lysophosphatidic acid (LPA) is a bioactive lysophospholipid that acts as an extracellular signaling molecule through six different G-protein-coupled receptors (LPA1-6). LPA signaling has many roles in the central nervous system that influence neural development, function, and behavior. Among LPA receptors, LPA1 is abundantly expressed in the brain. LPA1 deficient mice exhibit emotional dysregulation, impaired hippocampal-dependent memory and dysfunctional coping in response to chronic stress. Antidepressants have been reported as activating LPA1 signaling (Kajitani et al., 2016). Such findings indicate that LPA1 may be a potential therapeutic target for neuropsychiatric disorders. However, the cellular localization of LPA1 is not completely understood because of the lack of validated antibodies against LPA1. Here, we evaluated the cellular localization of LPA1 in the brain using LPA1 heterozygous mice that integrate a lacZ-reporter-tagged deletion allele. [Method] Current study used adult (> 6 week old) male Lpar1<tm1b(EUCOMM)Wtsi> mice, which contained a lacZ-reporter-tagged deletion allele in which the critical exon had been removed by Cre/loxP

mediated excision. LacZ (β-galactosidase) activity in a brain section was detected by X-Gal staining. Cellular localization of LPA1 in the brain was evaluated by double fluorescent immunostaining of antibodies against β-galactosidase and several cell markers (NeuN, DCX, GFAP, S100β, Olig2, Iba1, and CD31). [Results] X-Gal staining revealed that LacZ activity was observed in myelinated areas such as the corpus callosum. The distribution of LacZ activity was similar to a previous report that examined activity in situ through a LPA1 binding assay. Fluorescent immunostaining revealed that β-galactosidase-positive cells were enriched in the corpus callosum, but were sparsely observed in the whole brain area. The majority of β-galactosidase-positive cells expressed Olig2. The remaining β-galactosidase-positive cells expressed S100β, GFAP, and CD31. NeuN, DCX, and Iba1-positive cells hardly expressed β-galactosidase. [Conclusion] Several types of glial cells (oligodendrocytes and astrocytes), ependymal cells, and vascular endothelial cells express LPA1. LPA1 signaling may be involved in various activities of the brain network, including glial function and regulation of tissue fluids (blood and cerebrospinal fluid).

Disclosures: N. Kajitani: None. **M. Okada-Tsuchioka:** None. **H. Abe:** None. **W. Omori:** None. **K. Itagaki:** None. **M. Takebayashi:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.06/J13

Topic: B.11. Glial Mechanisms

Title: The cystine/glutamate antiporter system x_c^- as modulator of corticostriatal neurotransmission

Authors: *A. MASSIE[1], E. BENTEA[2,1], A. VILLERS[3], C. MOORE[4], A. FUNK[2], S. M. O'DONOVAN[2], L. VERBRUGGEN[1], E. DEPASQUALE[2], M. J. CHURCHILL[4], H. SATO[5], L. RIS[3], C. K. MESHUL[6,4], R. E. MCCULLUMSMITH[2]
[1]Vrije Univ. Brussel, Brussels, Belgium; [2]Univ. of Cincinnati, Cincinnati, OH; [3]Univ. of Mons, Mons, Belgium; [4]Portland VA, Portland, OR; [5]Niigata Univ., Niigata, Japan; [6]Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: The cystine/glutamate antiporter system x_c^-, with xCT as specific subunit, is mainly located on glial cells and couples the import of cystine with the export of glutamate. As such, system x_c^- contributes substantially to ambient extracellular glutamate levels in various regions of the brain, including the striatum and hippocampus. However, the physiological function of system x_c^- in the central nervous system remains poorly understood, despite its high expression in the brain. As a source of glial extrasynaptic glutamate, system x_c^- can affect synaptic neurotransmission as a mechanism of neuro-glial communication. In the current study, we

investigated how system x_c^- regulates transmission at corticostriatal synapses, one of the two major types of striatal excitatory synapses. Electrophysiological recordings identified a significant decrease in the amplitude of striatal field excitatory postsynaptic potentials in mice genetically lacking xCT ($xCT^{-/-}$ mice) following stimulation of corticostriatal fibers. Further, using electron microscopy, we observed depletion of glutamate immunogold labeling from corticostriatal terminals and their corresponding dendritic spines in $xCT^{-/-}$ mice. Genetic deletion of xCT did not, however, affect the morphology of corticostriatal synapses, the density of cortical innervation or spine density. Proteomic analysis of the striatum of $xCT^{-/-}$ mice revealed decreased expression of a wide range of proteins involved in regulating presynaptic neurotransmitter release, including synaptophysin, VGLUT1, and members of the synapsin, septin, and syntaxin families. In addition, kinome profiling identified changes in striatal serine/threonine kinase activity, highlighting ERK signaling as a possible node of kinase dysregulation in $xCT^{-/-}$ mice. Finally, in the marble burying test, a paradigm sensitive to changes in corticostriatal function, we measured a significant increase in repetitive digging behavior in $xCT^{-/-}$ mice. Together, our findings shed new light on the role of system x_c^- in controlling synaptic transmission. We hypothesize that the corticostriatal circuit deficits present in $xCT^{-/-}$ mice are a consequence of depletion of presynaptic glutamate stores, deficits in the presynaptic glutamate release machinery and/or aberrant ERK signaling, avenues we are currently exploring. As a novel modulator of corticostriatal transmission, system x_c^- may be relevant to neuropsychiatric disorders characterized by corticostriatal dysfunction and repetitive behavior, such as obsessive-compulsive behavior and autism.

Disclosures: A. Massie: None. **E. Bentea:** None. **A. Villers:** None. **C. Moore:** None. **A. Funk:** None. **S.M. O'Donovan:** None. **L. Verbruggen:** None. **E. Depasquale:** None. **M.J. Churchill:** None. **H. Sato:** None. **L. Ris:** None. **C.K. Meshul:** None. **R.E. McCullumsmith:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.07/J14

Topic: B.11. Glial Mechanisms

Support: NIH Grant R01EY013528

Title: Neuronal-Müller glial signaling in the developing retina

Authors: *J. M. TWORIG, M. B. FELLER
Univ. of California Berkeley, Berkeley, CA

Abstract: Müller glia are specialized radial astrocytes that are the predominant glial type of the vertebrate retina. Müller glia extend through each retinal layer and display fine filopodia-like

processes in synaptic layers. Prior to eye opening in the mouse, Müller glia respond to acetylcholine and glutamate released during retinal waves by undergoing calcium transients (Rosa et al, *J Neurosci*, 2016). Retinal wave-evoked glial calcium transients are compartmentalized to Müller glial stalks and processes in the inner plexiform layer, suggesting that the transients play a specific role in synaptic development or function.
Here, we address the mechanisms and function of Müller glial calcium transients during retinal development. First, we identify signaling pathways mediating wave-evoked calcium transients in Müller glia using simultaneous two-photon calcium imaging and electrophysiology. Blockade of M1 muscarinic acetylcholine receptors with pirenzepine (5 μM) or depletion of internal calcium stores with thapsigargin (5 μM) significantly reduced the proportion of Müller glia undergoing wave-evoked calcium transients. Second, we describe Müller glial process motility using two-photon volumetric imaging of fluorescently labeled Müller glia in the double reporter mouse line *GLAST-CreER;mTmG* (Wang et al, *J Comp Neurol*, 2017). We found that prior to eye opening, Müller glial lateral processes in the inner plexiform layer undergo bouts of extension and retraction, yet they are largely stable in the adult retina. We will test the hypothesis that acetylcholine or glutamate released during retinal waves modulates the outgrowth and/or motility of Müller glial processes.

Disclosures: J.M. Tworig: None. **M.B. Feller:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.08/K1

Topic: B.11. Glial Mechanisms

Support: NIH/NINDS Grant RO1NS083410
NSF GRFP DGE 1444316

Title: Microglial derived matrix metalloproteinases (MMPs) in synuclein mediated neuroinflammation

Authors: *K. SANCHEZ[1], K. A. MAGUIRE-ZEISS[2]
[1]Biol., Georgetown Univ., Washington, DC; [2]Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Matrix metalloproteinases (MMPs) are a family of endopeptidases that remodel the extracellular matrix and play an important role in synaptic plasticity. While MMPs have been evaluated in the context of synucleinopathies, their role in α-synuclein mediated neuroinflammation remains to be further characterized; specifically, in the context of glial-neuronal interactions. α-Synuclein is a 140-amino acid protein highly expressed in presynaptic

terminals that is also associated with Lewy body pathology found in Parkinson's (PD) patients. We and others have shown that α-synuclein is a damage-associated molecular pattern (DAMP) eliciting a microglial proinflammatory response through activation of pattern recognition receptors (PRRs). Furthermore, PD patients display increased expression of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β) as well as MMP-9.
Here we demonstrate that the expression of MMP-9 and MMP-13 are increased following exposure of microglia to mutant A53T α-synuclein. This increased MMP expression is associated with increased release of TNF-α and NF-κB nuclear translocation. The impact of MMP-13 and -9 on neurons remains to be further studied. Since MMPs are known to impact neuronal structure and survival, it is hypothesized that the release of MMP13 can impact neuronal structural plasticity. Future investigations will explore the impact of microglial-derived MMP13 on neurons and its cleavage targets such as PAR1. Specifically, we are interested in how dendritic complexity and cell viability of neurons is impacted by MMP-13.

Disclosures: K.A. Maguire-Zeiss: None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.09/K2

Topic: B.11. Glial Mechanisms

Support: T32-DA7288
R01-5369

Title: Transient plasticity of perisynaptic astrocyte processes during reinstated heroin seeking

Authors: *A. KRUYER[1], M. D. SCOFIELD[2], P. W. KALIVAS[3]
[2]Neurosci., [1]Med. Univ. of South Carolina, Charleston, SC; [3]Neurosci. Res., Med. Univ. S Carolina, Charleston, SC

Abstract: Repeated drug use, but not repeated exposure to natural rewards, disrupts glutamate homeostasis within corticofugal projections to the ventral striatum in response to reward-associated cues and contexts. Exposure to different classes of addictive drugs also results in downregulation of the principal glutamate transporter GLT-1, contributing to synaptic glutamate spillover and conferring relapse vulnerability. Synaptic proximity of perisynaptic astrocyte processes (PAPs) that contain GLT-1 affects the rate and efficiency of glutamate uptake, adding another measure of control over synaptic glutamate diffusion. We labeled astrocytes in the nucleus accumbens core (NAcore) with a membrane-targeted fluorescent tag. Using confocal microscopy, we measured synaptic proximity of PAPs via their colocalization with the pre-

synaptic marker Synapsin I. Using this strategy, we previously found that synaptic proximity of PAPs is reduced during extinction from cocaine self-administration. We found similar reductions in synaptic proximity of PAPs during extinction from heroin self-administration. We also observed rapid and reversible structural plasticity of NAcore astrocytes during 15-minutes of cued reinstatement, measured as reductions in volume and surface area, increased synaptic proximity of PAPs, and increased surface expression of GLT-1, despite reduced levels overall following heroin self-administration. These adaptations were restored to extinction levels by 120 minutes of reinstatement, when active drug seeking had ceased, and were not observed in NAcore astrocytes during reinstated sucrose seeking. Our findings suggest that NAcore astrocytes play a dynamic role in shaping glutamatergic transmission during cued drug seeking.

Disclosures: A. Kruyer: None. **M.D. Scofield:** None. **P.W. Kalivas:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.10/K3

Topic: B.11. Glial Mechanisms

Title: Microglial motility and interaction with dendritic spines is elevated in the hippocampus of awake mice due to increased neuronal activity

Authors: *F. C. NEBELING, S. POLL, L. C. SCHMID, J. STEFFFEN, K. KEPPLER, M. FUHRMANN
DZNE German Ctr. for Neurodegenerative Dis., Bonn, Germany

Abstract: Microglia, the resident immune cells of the CNS, actively survey their environment while interacting with other brain cells and structurally shaping the CNS. Yet, the mechanisms underlying microglial motility and their significance for structural plasticity, especially in adult organisms, remain widely unresolved. Here we investigated the impact of neuronal activity on microglia motility and its implication for synapse formation and survival in the hippocampus. Therefore, we implanted a chronic hippocampal-window in CX3CR1-GFP::Thy1-YFP-H transgenic mice. By applying two-photon microscopy, we were able to study microglia synapse interaction *in vivo* in adult mice. We recorded 3-D time series of microglia and synapses in the same mice sequentially under anesthesia and awake conditions. We found elevated microglia motility in awake compared to anesthetized mice. Furthermore, upon topical application of tetrodotoxin (TTX) in awake mice, microglial motility decreased below levels observed in anesthesia, indicating a relationship between neuronal activity and microglia motility. These findings were confirmed by injecting an inhibitory DREADD into CA3 and CA1, which enabled us to pharmacologically block neuronal activity in the *stratum radiatum* of awake mice. Chemogenetic inhibition of neuronal activity significantly reduced microglial motility in awake

mice. Thus neuronal activity seems vital for microglia motility. On the subcellular level, microglia showed increased synapse interaction in awake mice. We also observed elevated microglia motility around newly formed or eliminated dendritic spines compared to stable ones. Additionally, synapse turnover was more likely to be anatomically clustered in regions with high microglial contact rates. Overall, these findings suggest a neuronal-activity dependent regulation of synapse homeostasis in the hippocampus via microglia.

Disclosures: F.C. Nebeling: None. **S. Poll:** None. **L.C. Schmid:** None. **J. Stefffen:** None. **K. Keppler:** None. **M. Fuhrmann:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.11/K4

Topic: B.11. Glial Mechanisms

Support: EMBO ALTF 384-2015
ERC-2013-AD6; 339513
ANR/NSF 15-NEUC-0003-02
Fondation Leducq

Title: Vascular compartmentalization of functional hyperemia from the synapse to the pia

Authors: *R. L. RUNGTA, E. CHAIGNEAU, B.-F. OSMANSKI, S. CHARPAK
Lab. of Neurophysiol. and New Microscopies, INSERM U1128, Paris, Paris, France

Abstract: Functional hyperemia, a regional increase of blood flow triggered by local neural activation, is used to map brain activity in health and disease. Despite its vast importance for functional imaging, the spatial-temporal dynamics of functional hyperemia, as well as its site of initiation remain unclear. Here, we exploit the unique neural-vascular anatomy of the olfactory bulb and two-photon imaging in NG2-creERT2;GCaMP6f mice to investigate Ca^{2+} signaling and hemodynamics of functional hyperemia, from juxta-synaptic capillaries back to the upstream pia. We first show that activation of oligodendrocyte precursor cells (OPC) is a reliable marker of synaptic input and precedes (by ~300 ms) a synchronous Ca^{2+} drop in upstream pericytes and smooth muscle cells enwrapping the vessels that feed the activated synapses. Despite this simultaneous activation of mural cells, the resulting hemodynamics varied dramatically but precisely in terms of timing, amplitude and direction according to the vascular compartment. The most rapid dilation occurs with indistinguishable onset at the parenchymal arteriole and proximal first-order capillary and is paradoxically associated with a local decrease or delayed increase in blood velocity. In contrast, a slower dilation associated with a rapid velocity increase occurs in the upstream pial arteriole and downstream capillaries. Proportionally, the largest velocity

increase occurs in juxta-synaptic capillaries. These results establish the precise temporal and spatial dynamics of blood volume and velocity changes essential for the interpretation of blood flow based imaging techniques such as BOLD-fMRI.

Disclosures: R.L. Rungta: None. **E. Chaigneau:** None. **B. Osmanski:** None. **S. Charpak:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.12/K5

Topic: B.11. Glial Mechanisms

Support: CONACYT 255087

Title: Acute manganese exposure increases glutamate uptake in Bergmann glial cells

Authors: *M. ESCALANTE LOPEZ, L. C. R. HERNÁNDEZ KELLY, A. ORTEGA
Cinvestav, Mexico City, Mexico

Abstract: Even though manganese (Mn) is required as an essential trace element for humans, more public health concerns are focused on the adverse health impacts upon manganese exposure. Specifically, a cognitive and movement disorder, referred to as manganism. To date, Mn is reported to cause neurons as well as many other cell types functional impairments. Astrocytes, accounting for approximately 50% of the neuronal cells in the central nervous system and maintain glutamate homeostasis, are sensitive to neurotoxicity induced by Mn exposure. The fine regulation of extracellular glutamate in the brain is accomplished by two major glutamate transporters – GLT-1 and GLAST – that are predominantly expressed in astrocytes. Excitotoxic neuronal injury has been highlighted as a critical mechanism in Mn neurotoxicity and is also involved in the pathological signs of multiple neurodegenerative diseases including Amyotrophic Lateral Sclerosis, Alzheimer's disease and Parkinson’s disease.
Recent evidences demonstrate that Mn accumulates in different brain regions, including the cerebellum. Bergmann glial cells (BGC) are radial glial cells prevalent in the adult cerebellum and represent the most abundant non-neuronal population of this structure. This characteristic localization is related to their involvement in neurotransmitter uptake and turnover, K^+ homeostasis, lactate supply and pH regulation. Despite these well-known facts, little or null attention has been drawn to studying the role of BGC in Mn neurotoxicity.
To this end, in this contribution we focused in the molecular mechanisms induced by Mn that affect GLAST in BGC. A time and dose-dependent increase in GLAST activity was found upon acute Mn exposure. Moreover, Mn apparently modifies the amount of GLAST molecules in the plasma membrane, suggesting an alteration in its trafficking. In contrast to the reported findings

regarding GLAST regulation by Mn in cortical cell models, the kinetics of the Mn effects in neurogenic radial glia are faster and mediated through different signal transduction pathways. These results strengthen the notion of the critical involvement of radial glial cells in glutamatergic neurotransmission.

Disclosures: M. Escalante Lopez: None. **L.C.R. Hernández Kelly:** None. **A. Ortega:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.13/K6

Topic: B.11. Glial Mechanisms

Support: European Union's Seventh Framework Programme (FP7) under grant agreement No. 604102 (HBP RUP)
European Union's Horizon 2020 research and innovation programme under grant agreement No. 720270 (HBP SGA1)
Academy of Finland (decision No. 297893)

Title: In silico modeling of astrocytes and neuron-astrocyte interactions

Authors: *T. MANNINEN[1], A. SAUDARGIENE[2], R. HAVELA[1], M.-L. LINNE[1]
[1]BioMediTech Inst. and Fac. of Biomed. Sci. and Engin., Tampere Univ. of Technol., Tampere, Finland; [2]Neurosci. Inst., Lithuanian Univ. of Hlth. Sci., Kaunas, Lithuania

Abstract: Astrocytes have been shown to modulate information transmission and plasticity in several brain areas (Araque et al., 1999; Haydon and Nedergaard, 2015; Bazargani and Attwell, 2016). The mechanisms by which this modulation is orchestrated are however not understood (Fiacco and McCarthy, 2018; Savtchouk and Volterra, 2018). One reason for partially contradictory results is the lack of selective pharmacological tools for astrocytes (Bazargani and Attwell, 2016). In silico studies are one way to help solve the challenges related to experimental neuron-astrocyte interactions. In our previous studies (Manninen et al., 2017, 2018a-c), we have characterized and categorized a hundred computational models of astrocytes and neuron-astrocyte interactions as well as evaluated reproducibility and comparability of several models. Often new in silico models are published without explaining how they differ from the hundreds of previously published models and without giving all the model details. In addition, model implementations are rarely given in the online model repositories. All these make extension of models difficult. Models should be defined using common description formats in publications, implemented using easily accessible and expandable model description languages, and be downloadable via online model repositories. In this study, we extend our previously published neuron-astrocyte synapse model (Havela et al., 2017) with the description of presynaptic

terminal and gather the state-of-the-art experimental and computational knowledge of neuron-astrocyte interactions to help guide the future research of tripartite synapses. The here modeled presynaptic neurotransmitter release can induce elevated astrocytic calcium concentration, similarly to experimental in vitro data. Moreover, the elevated astrocytic calcium concentration can induce exocytosis of chemical substances from astrocytes which can modulate vesicle release from the presynaptic terminal. In addition to calcium signaling, we also address the endocannabinoid (eCB) signaling and explore the ability of the in silico model to modulate the presynaptic vesicle release by postsynaptic eCB system in contrast to astrocytic modulation. One of our future goals is to develop both detailed and reduced models of neuron-astrocyte interactions for different brain areas. With integration of both in vivo and in vitro data with corresponding in silico models, we might be able to explain which astrocytic mechanisms are important and how they contribute to brain information processing and plasticity. This will hopefully clarify the controversies in experimental data.

Disclosures: T. Manninen: None. **A. Saudargiene:** None. **R. Havela:** None. **M. Linne:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.14/K7

Topic: B.11. Glial Mechanisms

Support: PRIN 2015-2015W729WH_005 to ATP and GDC

Title: ATP released from astrocytes mediates herpes simplex virus type 1 (HSV-1) infection in neurons

Authors: *R. PIACENTINI[1], D. D. LI PUMA[1], M. E. MARCOCCI[3], G. LAZZARINO[2], G. DE CHIARA[4], C. RIPOLI[1], B. TAVAZZI[2], A. T. PALAMARA[3,5], C. GRASSI[1]
[1]Inst. of Human Physiol., [2]Inst. of Biochem. and Clin. Biochem., Univ. Cattolica, Med. Sch., Rome, Italy; [3]Dept. of Publ. Hlth. and Infectious Diseases, Pasteur Institute, Fondazione Cenci Bolognetti, Sapienza Univ. of Rome, Rome, Italy; [4]Inst. of Translational Pharmacol., Natl. Res. Council, Rome, Italy; [5]San Raffaele Pisana, IRCCS, Rome, Italy

Abstract: Astrocytes play several functions in the brain: they give structural and metabolic support to neurons and modulate synaptic transmission by the release of gliotransmitters including ATP. Here we asked whether astrocytes also have a “dark side”, specifically contributing to HSV-1 infection of neurons. HSV-1 (1 MOI) was applied for 1 h (adsorption time) to co-cultures of mouse cortical neurons and astrocytes to allow virus binding and entry into cells. After 24 h, infection was assessed by immunocytochemistry and Western blot analysis of viral proteins. We observed that astrocytes were more susceptible than neurons to HSV-1

infection, in agreement with our finding that astrocytes exhibit 4-fold greater expression of Heparan Sulfate Proteoglycans (binding sites for viral glicoproteins C and B) than neurons ($p<0.05$). The probability to find HSV-1-infected (HSV-1^+) neurons was significantly higher in proximity (<100 µm) of virus-infected astrocytes. At such distance about 78±6% of neurons were HSV-1^+ vs. only 11±6% of neurons far from HSV-1^+ astrocytes ($p<0.05$). When co-cultures were challenged with HSV-1 after metabolic inhibition of astrocytes by fluorocitrate (FC, 200 µM), neither astrocytes nor neurons were HSV-1^+, thus suggesting that the presence of functional astrocytes is necessary for neuronal virus infection. HSV-1 binding to astrocytic plasma membrane triggered IP3-dependent intracellular Ca^{2+} transients followed by ATP release, whose concentration in the culture medium, assessed by HPLC, was up to 4-fold higher than that of control cultures (44.1±11.3 vs. 10.3±1.2 nM; $p<0.05$). ATP released from astrocytes diffused locally and activated purinergic P2 receptors (P2R) on neurons and astrocytes themselves that sustained and amplified Ca^{2+} transients. Application of the P2R blocker suramin (200 µM) during the adsorption time prevented HSV-1 infection, thus suggesting that ATP released from astrocytes and the consequent P2R-dependent Ca^{2+} transients are necessary for virus infection of both astrocytes and neurons. Accordingly, if exogenous ATP (100 µM) was applied to FC-treated co-cultures during the adsorption time more than 70% of neurons was HSV-1^+ after 24 h. ATP-induced P2R-mediated Ca^{2+} transients caused activation of the Glicogen Synthase Kinase (GSK)-3 by phosphorylation at Y216 in both astrocytes and neurons, and GSK-3 inhibition by SB216763 (10 µM) during the adsorption time completely prevented HSV-1 infection. In conclusion, we found that ATP released from astrocytes after HSV-1 binding diffuses locally and causes P2R-dependent activation of GSK-3 in both neurons and astrocytes, likely involved in HSV-1 infection.

Disclosures: D.D. Li Puma: None. **M.E. Marcocci:** None. **G. Lazzarino:** None. **G. De Chiara:** None. **C. Ripoli:** None. **B. Tavazzi:** None. **A.T. Palamara:** None. **C. Grassi:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.15/K8

Topic: B.11. Glial Mechanisms

Support: NSF

Title: Octopus glia: Identification of glia-specific molecular markers in cephalopods

Authors: *G. C. WINTERS[1], H. E. WEBER[2], C. J. BOSTWICK[1], L. L. MOROZ[1]
[1]Neurosci., Univ. of Florida Whitney Lab. for Marine Biosci., Saint Augustine, FL;
[2]Transylvania Univ., Lexington, KY

Abstract: Cephalopods (*Octopus*, Squid, Cuttlefish, and *Nautilus*) exhibit a degree of behavioral flexibility comparable to that of many mammals. The intricate neural circuits responsible for this behavioral complexity have evolved in parallel to arthropod and chordate nervous systems. The independent emergence of sophisticated brains in distinct lineages has produced a natural subject of investigation to understand physiological, anatomical, and molecular constraints of nervous system evolution. Despite diverse interdisciplinary efforts to characterize *Octopus* brain circuitry, little is known about the enigmatic support cells of the nervous system: glia. Although glia-like cells have been recognized based on anatomical position and morphology in *Octopus* brains and peripheral neural tissues, no molecular markers for cephalopod glia have been identified. There has been no evidence for sequences encoding mammalian glial markers such as GFAP and vimentin in any available cephalopod transcriptomes. We constructed, sequenced, and analyzed *Octopus bimaculoides* transcriptomes of 85 tissues (neuronal and peripheral) to identify conserved and novel molecules expressed in *Octopus* neurons and glia. Abundant transcripts from neuronal transcriptomes were anatomically validated using *in-situ* hybridization. Of the 167 transcripts we investigated, seven were expressed in cells morphologically resembling glia. Two of these putative glial molecules were enzymes associated with neurotransmitter synthesis or metabolism (glutamate decarboxylase and glutamine synthetase- a molecule that also labels mammalian glia), and five were novel predicted secretory molecules. Aside from a conserved eukaryotic glycoprotein, each of the putative glial secretory molecules is either mollusc-specific or unique to cephalopods. Cellular expression maps of each marker vary by distribution, density, and reveal four different morphologically distinct types of glia-like cells. The combination of evolutionarily conserved and cephalopod-specific genes, which are uniquely expressed in *Octopus* glia suggests three possible scenarios for glia specification: (1) independent recruitment of conserved proteins (glutamine synthetase) in novel cephalopod cell types, (2) development of novel secretory molecules in evolutionary conserved glial-like cell lineages, and/or (3) multiple origins of cephalopod glial sub-populations.

Disclosures: G.C. Winters: None. **H.E. Weber:** None. **C.J. Bostwick:** None. **L.L. Moroz:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.16/K9

Topic: B.11. Glial Mechanisms

Support: Brain Canada with the W. Garfield Weston Foundation
Natural Sciences and Engineering Research Council of Canada
Canadian Institutes of Health Research
Canadian Foundation for Innovation

Research Institute of the McGill University Health Centre

Title: Forebrain GABAergic neurons regulate astrocyte gene expression through the morphogen sonic hedgehog

Authors: *W. T. FARMER[1], S. CHIERZI[1], G. CHEN[2], J.-F. THÉROUX[2], C. ERNST[2], K. K. MURAI[1]
[1]Ctr. for Res. in Neurosci., [2]Dept. of Psychiatry, McGill Univ., Montreal, QC, Canada

Abstract: Astrocytes are a heterogeneous population of cells that are critical for maintaining the precise environmental conditions required for optimal neuronal activity. To faithfully fulfill diverse roles across the central nervous system, astrocytes display a complex range of specialized physiological and molecular phenotypes. Despite the importance of astrocyte specialization for nervous system function, the processes responsible remain poorly understood. Previously, we have shown that the morphogen Sonic Hedgehog (Shh) is secreted by neurons to regulate the expression of the inward rectifying potassium channel Kir4.1/KCNJ10 in forebrain astrocytes. To further our understanding of astrocyte specialization in the adult forebrain, we aimed to identify the genes regulated by the Shh pathway as well as the specific neuron populations that are responsible for Shh release in both the hippocampus and the medial septum/diagonal band complex (MSBD). To reveal genes that are regulated by the Shh pathway, we performed RNA-seq on control hippocampi and hippocampi containing astrocytes with the Shh pathway constitutively-activated. Differential gene expression analysis revealed that the Shh pathway regulates a cohort of ~500 genes, many of which are ion channels and neurotransmitter transporters known to influence neural activity including the GABA transporter Slc6a11/GAT3. Interestingly, the cohort of genes regulated in the hippocampus is distinct from the genes previously identified in the cerebellum. To identify Shh-expressing cells, we utilized an inducible Cre-dependent Shh expression reporter system. In the adult hippocampus and MSBD, reporter expression was detected predominantly in mixed populations of GABAergic neurons. To evaluate the contribution of GABAergic neurons to both Shh expression levels and astrocyte gene expression, we utilized the GAD2-Cre allele to specifically knock out Shh from GABAergic neurons (GAD2 cKO). Quantitative PCR and immunofluorescence on GAD2 cKO knockout brains revealed a robust reduction of Shh message and significant changes in the expression of Shh-responsive genes in both the hippocampus and MSBD. These results show that GABAergic neurons are responsible for regulating specific aspects of astrocyte gene expression through the release of Shh. Furthermore, neuron-astrocyte communication through Shh appears to be widely used across the brain to fine-tune the molecular properties of astrocytes in a region-specific manner.

Disclosures: S. Chierzi: None. **G. Chen:** None. **J. Théroux:** None. **C. Ernst:** None. **K.K. Murai:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.17/K10

Topic: B.11. Glial Mechanisms

Support: NIH/NIDCD R01 DC007695
NIH/NIGMS P30 GM103503

Title: Characterization of the initial stages of myelination in the medial nucleus of the trapezoid body

Authors: *D. T. HELLER[1,2], D. KOLSON[1], A. BRANDEBURA[2], J. WAN[4], J. QIAN[5], P. MATHERS[3], G. A. SPIROU[6]
[1]Otolaryngology, West Virginia Univ., Morgantown, WV; [2]Otolaryngology, [3]Biochem., West Virginia Univ. Sch. of Med., Morgantown, WV; [4]Indiana Univ. Sch. of Med., Indianapolis, IN; [5]Johns Hopkins, Baltimore, MD; [6]Otolaryngology, West Virginia Univ. Sch. Med., Morgantown, WV

Abstract: Glial cells play a major role in regulating synaptogenesis, cell proliferation and differentiation, and myelination during neural circuit formation and maturation. Myelination is a complex process involving the targeted compartmentalization of several myelin-associated proteins resulting in the wrapping of axons. Astrocytes play a functional role in myelination by regulating oligodendrocyte proliferation and differentiation, providing lipids for myelin synthesis, and promoting myelination in response to electrical activity. Several studies have shown that astrocytes promote myelination, but the exact functions associated with astrocyte-axonal interactions remains elusive. The medial nucleus of the trapezoid body (MNTB) is used as a model system for studying neural circuit formation and maturation. The large presynaptic nerve terminals onto MNTB neurons, the calyces of Held, grow very quickly between postnatal day (P)2 and P6 and are mostly refined to mono-innervation within the first postnatal week. Furthermore, the astrocytes and oligodendrocytes in the MNTB increase in number and begin to exhibit morphological maturation within the same time window, allowing for a detailed study of the coordinated role of astrocytes and oligodendrocytes in myelination. Limitations associated with the resolution of fluorescence microscopy hamper detailed structural analysis of the myelin sheath and the extent of myelination. For this study, an extensive collection of serial block-face electron microscopy (SBEM) data sets from the mouse MNTB at P2, P4, P6, and P9 were used. These volumes allowed for the detailed investigation of individual calyceal axons, which elucidated ultrastructural characteristics of the onset and progression of axonal wrapping and myelin compaction during early development. Many of the calyceal axons were receiving single glial wraps by P4 with compaction of the myelin sheath beginning at P6, after most MNTB

principal neurons are mono-innervated. From the analysis of our SBEM volumes, we find that the early axonal wrapping at P4 originate from astrocyte-like cells while oligodendrocytes do not begin wrapping until P6. Gene expression profiles from our microarray study of the MNTB between P0-P14 provide a temporal sequence of expression onset for myelination-related genes, with expression profiles turning on four to six days before compaction of myelin. This study provides a genetic and structural basis for future research investigating the coordinated roles of glial cells in myelination.

Disclosures: D.T. Heller: None. **D. Kolson:** None. **A. Brandebura:** None. **J. Wan:** None. **J. Qian:** None. **P. Mathers:** None. **G.A. Spirou:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.18/K11

Topic: B.11. Glial Mechanisms

Title: Aloe vera colon fermentation compounds suppresses the substance P-induced production of IL-6 and IL-8 by human U373MG glioblastoma/astrocytoma cells

Authors: *A. TORNERO
Inst. Politecnico Nacional, Ciudad de Mexico, Mexico

Abstract: Introduction: In recent years there has been an increased incidence of neurodegenerative diseases around the World. Functional food has demonstrated beneficial effects against some pathological markers of brain degeneration, such as neuroinflammation. Aloe vera is a plant rich in polysaccharides (PA) with proven anti-inflammatory properties in vivo and in vivo studies, resulting in an improved health status in diseases associated conditions. Moreover, A. vera presents well known neuroprotective activities. PA are avidly taken up by gut microbiota (GM) that metabolize them, and release potent anti-inflammatory compounds, such as short-chain-fatty acids (SCFAs). However, the neuroprotective effects of SCFAs produced from A. vera fermentation has not been reported. **Methods:** In the present study we incubated human faecal samples with homogenates of inner gel and the PA fraction of A. vera. An in vitro digestion method, was followed by fermentation during 48 hrs. We collected fermented samples every 2 hours to determine the anti-oxidant activity and the presence of SCFAs (acetate, propionate,butyrate). Thereafter, those fermented fractions were added to human astrocytoma cell line, U373MG activated with neuropeptide substance P (SP). The U373MG cells were plated into 12-well tissue culture plates at a density of 2x105 cells/well and incubated in MEM supplemented with 10% FBS for 12 h, followed by incubation in MEM supplemented with 0.5% FBS for 12 h at 37℃. Subsequently, the cells were incubated with the different digested fraction of (0.1 and 1 mM) for 60 min, and then stimulated with SP (100 nM) for 10 min or 24 hr. We

used western-blot analysis for quantification of ERK1/2, p38 MAPK and NF-κB proteins. Analysis and IL-6 and IL-8 levels was done by use of Cytometric Bead Array Human Inflammatory Cytokine kit (BD Biosciences). **Results:** We observed that a higher anti-oxidant activity in the inner gel compared to PA fraction. However, the digested PA fraction presented a potent anti-inflammatory effect on U373MG cells, associated with an increased abundance of SCFAs that increases along the fermentation period. **Conclusion:** This study demonstrates that A. vera neuroprotective properties may be associated with GM´s fermentation of polysaccharides and subsecuente release of SCFAs with strong anti-inflammatory effects.

Disclosures: A. Tornero: None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.19/K12

Topic: B.11. Glial Mechanisms

Support: NIH R15NS095314
NSF-MRI DBI0821211
Plexxikon for supplying PLX5622 diet

Title: Effects of microglia elimination in the spinal cord on glial plasticity observed following peripheral axon injury

Authors: *J. HUTCHINSON[1], J. GOINS[1], V. RAJATHI[2], L. G. ISAACSON[3]
[1]Biology, Ctr. for Neurosci. and Behavior, [2]Cell, Mol. and Structural Biol., [3]Biology, Ctr. for Neurosci. and Behavior, Cell, Mol. and Structural Biol., Miami Univ., Oxford, OH

Abstract: Our lab has previously shown that transection of preganglionic axons of the cervical sympathetic trunk (CST) in the periphery results in robust activation of glial cells within the intermediolateral cell column (IML) of the spinal cord near the vicinity of the injured cell bodies. One week post injury, activated microglia are observed within the IML, characterized by increased expression of Iba1, cellular aggregation, and amoeboid like morphology. Because microglia-derived cytokines signal to nearby glial cells, we aimed to eliminate microglia in the mouse spinal cord to investigate their role in oligodendrocyte (OL) lineage cell and astrocyte plasticity as well as in cytokine expression following peripheral axon injury. We previously reported that use of the PLX5622 diet (Plexxikon), which contains colony stimulating factor-1 receptor (CSF-1R) inhibitor, successfully eliminated approximately 90% of microglia in young adult C57BL/6 mice spinal cord. Oligodendrocyte progenitor cells (OPCs) were increased in Sham+PLX group (vs Sham+Cont), suggesting that microglia influence baseline OPC proliferation. In addition, elimination of microglia reduced the typical increase in OPCs observed

post injury, indicating that microglia positively influence OPC plasticity. The absence of microglia did not affect CC1 or Olig2 cells, indicating no changes in mature oligodendrocyte populations. GFAP immunofluorescence revealed that microglia elimination did not affect the typical astrocyte activation observed post injury. Western blot analysis revealed no change in GFAP protein in Sham+PLX compared with Sham+Cont and did not detect an increase post injury in the control group. However, GFAP protein expression in the IML was increased by approximately 37% in the Inj+PLX group compared to Sham+PLX, indicating a more robust response to peripheral axon injury in the absence of microglia, and suggesting that microglia regulate astrocyte activation post injury. Interleukin-1ß (IL-1ß) was expressed by astrocytes in the mouse spinal cord. Following injury, IL-1β in the spinal cord was upregulated in Inj+Cont mice, yet this increase was blunted when microglia were eliminated, suggesting a role for microglia in the upregulation of pro-inflammatory cytokines in astrocytes at 1 week post injury. These findings indicate that microglia play an important role in the regulation of OL lineage cells and astrocytes in the mouse spinal cord. Overall, these results lead to a better understanding of the influences of microglia within the spinal cord microenvironment in the intact animal as well as following peripheral axon injury.

Disclosures: J. Hutchinson: None. **J. Goins:** None. **V. Rajathi:** None. **L.G. Isaacson:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.20/K13

Topic: B.11. Glial Mechanisms

Support: NIH R15NS095314
NSF-MRI DBI0821211

Title: Sequential analysis of glial cell plasticity in the spinal cord following peripheral axon injury

Authors: *V. RAJATHI[1], S. BHATI[1], S. P. BROWN[2], J. GOINS[3], J. HUTCHINSON[3], L. G. ISAACSON[4]
[1]Cell, Mol. and Structural Biol., [2]Biol., [3]Biology, Ctr. for Neurosci. and Behavior, [4]Biology, Ctr. for Neurosci. and Behavior, Cell, Mol. and Structural Biol., Miami Univ., Oxford, OH

Abstract: Following transection of the cervical sympathetic trunk (CST), we have previously reported robust glial cell plasticity in the intermediolateral (IML) cell column of the spinal cord in close proximity to the injured parent cell bodies. At 7 days following CST transection, we observe increased numbers of activated microglia and astrocytes, as well as an increase in oligodendrocyte lineage cells in the IML and adjacent white matter (WM). Both microglia and

oligodendrocyte precursor cell (OPC) proliferation contribute to this glial cell plasticity. However, the sequence of events that takes place in the IML and WM during the 7 day post injury period remains unclear. The objective of this study was to compare glial cell activation and proliferation in the rat spinal cord at 3 days and 7 days post injury. Starting on the day of the CST transection or sham surgery, young adult female Sprague Dawley rats were given daily ip injections of bromodeoxyuridine (BrdU; 20mg/ml in sterile saline solution) for either 3 or 7 days and sacrificed 24 hours after the last BrdU injection. The IML and WM of the upper thoracic spinal cord were analyzed, using immunofluorescence, for changes in microglia activation and proliferation. In the IML similar increases in the number of $Iba1^+$ cells, $BrdU^+$ cells, and $BrdU^+/Iba1^+$ cells, were observed at 3 days and 7 days post injury (vs respective shams), indicating that microglia proliferation in the IML was similar at the two post injury time points. However, in the WM, the number of $BrdU^+$ cells and $BrdU^+/Iba1^+$ cells, while unchanged at 3 days post injury, was significantly increased at 7 days post injury (vs respective shams), suggesting that changes in glial cell plasticity in the WM take place after day 3 of the post injury survival period. Cytokine analysis of cores taken from IML and adjacent WM of rat spinal cord at 3 days or 7 days post injury revealed similar increases in ciliary neurotrophic factor (CNTF) and CXCL7 (vs sham). However, a two-fold increase in the expression of intercellular adhesion molecule-1 (ICAM-1; CD54) was observed at 7 days with no change observed at 3 days post injury (vs sham). The increase in ICAM-1 at 7 days post injury may reflect the additional plasticity taking place in the WM late in the 7 day survival period. Further investigation will indicate whether sequential changes occur in the OPCs between 3 and 7 days post injury. Together our results will provide evidence regarding the timing of proliferation and cell signaling events that take place in the spinal cord following peripheral axon injury, and may provide important clues to how glial plasticity ultimately impacts neuronal survival.

Disclosures: V. Rajathi: None. **S. Bhati:** None. **S.P. Brown:** None. **J. Goins:** None. **J. Hutchinson:** None. **L.G. Isaacson:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.21/K14

Topic: B.11. Glial Mechanisms

Support: NIH NS095314
NSF-MRI DBI-0821211

Title: Effects of minocycline administration on the superior cervical ganglion following transection of the cervical sympathetic trunk

Authors: *R. SNYDER[1], M. POWELL[2], J. GOINS[2], L. G. ISAACSON[3]
[1]Biol., [2]Biology, Ctr. for Neurosci. and Behavior, [3]Biology, Ctr. for Neurosci. and Behavior, Cell Mol. and Structural Biol., Miami Univ., Oxford, OH

Abstract: The transection of distal axons in the cervical sympathetic trunk (CST) leads to robust retrograde neuronal and glial plasticity in the upper thoracic spinal cord. One week post injury the parent sympathetic preganglionic neurons housed in the intermediolateral cell column (IML) exhibit transient plasticity, including decreased expression of choline acetyltransferase (ChAT), and the nearby microglia, astrocytes, and oligodendrocyte (OL) lineage cells in the IML increase in number and show robust activation. Previously we reported that dampening microglia activation using the antibiotic minocycline (Mino) reversed the typical decrease in ChAT expression in young adult Sprague-Dawley rats, and also reduced the number of astrocytes and OLs in the IML typically observed at one week post injury. In a second group of rats examined four months post injury, fewer ChAT neurons were present in the IML of the Inj+Mino group, suggesting that dampened glial activation and reduced neurotransmitter plasticity by the injured neurons during the one week post injury contributed to long-term neuronal loss. Here we examined the superior cervical ganglion (SCG), the sole target of the transected CST axons, at one week and 4 months post injury to assess whether minocycline administration during the first week post injury affected peripheral macrophages in the ganglion or long term reinnervation of the SCG. Starting on the day of surgery Sprague-Dawley rats received daily ip injections of Mino (50mg/kg for 2 days; 25mg/kg for 5 days) or vehicle (VEH; saline; 2ml/kg) for one week following bilateral CST transection or sham surgery. Rats were examined at one week (Sham+VEH, n=4; Inj+VEH, n=3; Sham+Mino, n=4; Inj+Mino, n=2) and 4 months post injury (Sham+VEH, n=8; Inj+VEH, n=9; Sham+Mino, n=8; Inj+Mino, n=10). At one week post injury the number of macrophages (Iba1+) as well as macrophages per neuron (labeled with NeuN) were increased in the Inj+VEH group (vs Sham+VEH). However these increases were blunted in the Inj+Mino group (vs Sham+Mino), suggesting that minocycline treatment reduced the number of peripheral macrophages in the SCG following injury. Additionally, both ChAT and synaptophysin were virtually eliminated in the SCG in both injury groups at one week and no changes in NeuN+ neurons were observed. At 4 months post injury SCGs from both Inj+VEH and Inj+Mino groups showed approximately 50% ChAT and 76% synaptophysin reinnervation, indicating that Mino treatment did not affect the reinnervation of the SCG. We conclude that minocycline administration can impact both microglia and peripheral macrophages. However, these changes did not impact long term reinnervation of the SCG.

Disclosures: R. Snyder: None. **M. Powell:** None. **J. Goins:** None. **L.G. Isaacson:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.22/K15

Topic: B.11. Glial Mechanisms

Support: NIH Grant R01AG041944

Title: Aging and an immune challenge interact to potentiate activation of hippoccampal microglia in a rodent model with features of delirium

Authors: *N. SALLA, K. C. ESSLINGER, L. M. DEFLITCH, N. TANAKA, S. L. PATTERSON
Dept. of Biol., Temple Univ., Philadelphia, PA

Abstract: Aging increases the risk of an abrupt cognitive decline, sometimes called delirium, following an injury or illness. Although little is known about why aging brains are more vulnerable to immune stressors, research has shown that the immune and central nervous systems communicate extensively. Data drawn from rodent models suggest that microglia, cells of the innate immune system, become primed (sensitized) with age, responding more vigorously to signals from the peripheral immune system and other parts of the brain. Fischer Brown Norway (F344xBN) rats display no significant physical or cognitive impairments at 24 months. However, in response to a single intraperitoneal injection of *E. coli*, microglial production of proinflammatory cytokines is potentiated and prolonged in the aged (24 months) rats compared to production in their younger (3 months) counterparts. We have previously demonstrated that these aged animals have deficits in hippocampus-dependent long-term memory and memory-related synaptic plasticity that mirror the elevations in proinflammatory cytokines. We are now more closely examining the involvement of microglial dysregulation in these aging-associated, immune-challenge driven cognitive deficits. We are using immunohistochemistry for IBA1, a microglial membrane protein, to compare microglial numbers, distribution, and morphological changes triggered by a peripheral immune challenge in old and young animals with or without a recent history of *E. coli* infection. Preliminary findings indicate that IBA1 labeling is increased in the aged compared to young animals, and this trend is more pronounced following infection. In addition, there appear to be distinctive morphological profiles associated with microglia in the infected vs. saline groups and aged vs. young groups. We are also examining IBA1 expression in different subregions of the hippocampus and at different times after infection. Analysis of microglial phenotypes over time allows us to assess potential changes in microglial phenotypes. Prolonged activation is consistent with the idea that the dysregulation of the immune system may play a significant role in an abrupt cognitive decline and possibly in progression to dementia. We are developing novel algorithms for quantitative analysis of microglial numbers and morphology in specific pixel ranges. By comparing the number of microglia in each differing pixel ranges, we are investigating the relative distributions of IBA1 cluster sizes across treatment groups. Through these distributions we are attempting to categorize morphological profiles of microglia across these treatment groups.

Disclosures: N. Salla: None. **K.C. Esslinger:** None. **L.M. DeFlitch:** None. **N. Tanaka:** None. **S.L. Patterson:** None.

Poster

651. Glial-Neuron Interactions

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 651.23/K16

Topic: B.11. Glial Mechanisms

Support: 5R01AG041944

Title: Aging and an immune challenge result in increased activation of microglial complement proteins in the rat hippocampus

Authors: *A. S. ARNOLD, C. R. FITZGERALD, L. G. RODRIGUES, J. D. WEIR, N. TANAKA, S. L. PATTERSON
Biol., Temple Univ., Philadelphia, PA

Abstract: Aging significantly increases brain vulnerability to negative life events. Cognitive function in older individuals often declines precipitously after events (surgery, infection, or injury) that trigger activation of the immune system. This impairment is often temporary, but its occurrence is associated with a greatly increased probability of eventually developing Alzheimer's disease or other forms of dementia. Very little is known about the underlying mechanisms. However, since the immune and central nervous systems communicate extensively, it seems likely that dysregulation of brain immune cells (particularly microglia) may contribute to immune-challenge evoked cognitive impairment.

Aging is known to sensitize microglia to signals triggered by immune challenges, resulting in an exaggerated production of pro-inflammatory cytokines like IL-1β. Aged (24-month-old) Fischer Brown Norway (F344xBN) rats are generally healthy, with no significant physical or cognitive impairments. However, in response to a single i.p. injection of *E. coli*, production of IL-1β is potentiated and prolonged in the aged (24 months) rats compared to production in their younger (3 months) counterparts. We have previously demonstrated that these aged animals have deficits in hippocampus-dependent long-term memory and memory-related synaptic plasticity that mirror the elevations in proinflammatory cytokines.

In addition to producing chemical mediators of immune function like IL-1β, microglia can also act as phagocytes, engulfing foreign invaders. Intriguingly, they have also been shown to play a role in developmental synaptic pruning and remodeling. Proteins of the complement cascade interact with pathogens, or with inappropriate or under performing synapses to mark them for destruction by phagocytes. We have now begun to explore the possibility that microglia may also play a more direct role in immune-challenge driven cognitive impairment.

Using immunohistochemistry, we are investigating the presence and interactions of proteins associated with phagocytic activity, including those within the complement cascade (e.g. C3 and C1q). Our preliminary data suggest that C3 labeling is increased in rats with a recent history of

infection, and this trend is more pronounced in aged animals. We are also examining distribution and expression levels of these proteins in different hippocampal regions. A time-course study will be conducted to determine if changes in the expression of these immune markers persist in parallel with deficits in synaptic plasticity.

Disclosures: A.S. Arnold: None. **C.R. Fitzgerald:** None. **L.G. Rodrigues:** None. **J.D. Weir:** None. **N. Tanaka:** None. **S.L. Patterson:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.01/K17

Topic: B.11. Glial Mechanisms

Title: Specific MHCI overexpression in astrocytes induces behavioral and neuropathological abnormalities in mice

Authors: *K. HADA[1], A. SOBUE[1], B. WULAER[1], N. ITOH[1], A. NAKAJIMA[1], T. NABESHIMA[2,3], T. NAGAI[1], K. YAMADA[1]
[1]Nagoya Univ. Grad. Sch. of Med., Nagoya/Aichi, Japan; [2]Advanced Diagnos. Syst. Res. Lab. Fujita Hlth. University, Grad. Sch. of Hlth. Sci., Toyoake/Aichi, Japan; [3]Aino Univ., Ibaraki/Osaka, Japan

Abstract: Major histocompatibility complex class I (MHCI) molecules play an important role in the adaptive and innate immune responses, and MHCI genes are polygenic and highly polymorphic. Classical MHCI α-chains in humans are encoded by three genes, HLA-A, B, and C, while their homologues are H-2K, D, and L in mice. The unique roles of MHCI molecules have been demonstrated in the central nervous system. Association studies have also implicated MHCI genes in several neuropsychiatric disorders such as Parkinson's disease, Alzheimer's disease and schizophrenia. However, the pathophysiological role of astroglial MHCI in neuropsychiatric disorders remains unclear. We have previously reported that polyriboinosinic-polyribocytidylic acid (polyI:C) treatment in neonatal mice results in impairments of neurodevelopment accompanied by schizophrenia-like behaviors in adulthood. Neonatal polyI:C treatment in mice increased MHCI H-2K and H-2D mRNA levels mainly in astrocytes but not neurons in the medial prefrontal cortex (mPFC). Moreover, we have previously demonstrated the localization and secretion of MHCI/H-2D and its soluble form (sH-2D) as exosomes in cultured astrocytes. To clarify the role of MHCI in astrocytes, we developed a mouse model expressing MHCI molecules in astrocytes of mPFC, using an adeno-associated virus vector (AAV) that expresses the transgene under the control of glial fibrillary acidic protein (GFAP) promoter. Behavioral and neuropathological analyses were carried out 3 weeks after the AAV injection. The MHCI-expressing mice showed impaired sociability and cognitive function. Additionally,

the number of Iba1-positive microglial cells was significantly increased in the mPFC of MHCI-expressing mice compared with control mice. Astroglial expression of MHCI decreased the number of parvalbumin-positive cells and reduced the dendritic spine density of pyramidal neurons in the mPFC. Furthermore, repeated treatment of neutral-sphingomyelinase inhibitor GW4869 ameliorated these abnormal behaviors and neuropathological changes observed in MHCI-expressing mice. These results suggest that the exosomal MHCI derived from astrocytes affects the microglial proliferation as well as neuronal number and spine density, thereby leading to behavioral dysfunctions in mice.

Disclosures: K. Hada: None. **A. Sobue:** None. **B. Wulaer:** None. **N. Itoh:** None. **A. Nakajima:** None. **T. Nabeshima:** None. **T. Nagai:** None. **K. Yamada:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.02/K18

Topic: B.11. Glial Mechanisms

Support: Helmsley Postdoctoral Fellowship
Catharina Foundation Postdoctoral Fellowship

Title: Novel astrocyte-secreted factor promotes synapse maturation and limits plasticity through GluA2-AMPAR clustering

Authors: *E. BLANCO SUAREZ, T. LIU, A. KOPELEVICH, N. J. ALLEN
MNL, Salk Inst. For Biol. Studies, La Jolla, CA

Abstract: Astrocytes are the most abundant glial cells in the mammalian brain. Among their various functions, astrocytes secrete factors that affect the number and strength of synapses. Some of these factors regulate the subunit composition of AMPA glutamate receptors (AMPARs), the main transducers of fast excitatory neurotransmission in the mammalian brain. AMPARs are di-heteromers composed of GluA1-4 subunits, which vary in subunit composition depending on the stage of development. GluA1-containing AMPARs are extensively expressed at the synapses in early stages of development, clustered by glypican 4 and 6, astrocyte-secreted factors previously identified by our lab. They are subsequently replaced by GluA2-containing AMPARs in order to promote synaptic maturation in the mouse brain. However, the mechanism behind this switch remains unknown. Identifying the astrocytic factor that promotes the expression of GluA2 at the synapse has important implications for normal synapse formation, maturation and synaptic plasticity. By biochemical screening, we identified a novel astrocyte-secreted factor that is sufficient to enrich synaptic levels of GluA2, increase synapse number and enhance synaptic function between neurons *in vitro*. This novel astrocyte factor has

heterogeneous temporal and regional expression in the mouse brain, but is enriched in the visual cortex at the time of synapse maturation. KO mice for the astrocyte-secreted factor showed decrease in GluA2 and altered kinetics of synaptic transmission *in vivo*. These are features of immature synapses that promote higher brain plasticity. Experience-dependent plasticity in the visual cortex of the KO mice was enhanced, in both critical period and later when the visual cortex circuitry is fully developed and stable. These results indicated that the astrocyte-secreted factor is key to limit plasticity, and its role is not restricted to development and synapse maturation, but throughout life. Understanding astrocyte-secreted factors in the context of synaptic formation and plasticity in the brain will help to define the role of astrocytes in synapse formation, and synaptic maturation, but also to elucidate new avenues to manipulate synaptic plasticity, especially at later stages in life when it greatly declines.

Disclosures: E. Blanco Suarez: None. **T. Liu:** None. **A. Kopelevich:** None. **N.J. Allen:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.03/L1

Topic: B.11. Glial Mechanisms

Support: NSERC 195814317

Title: Contribution of astrocytic purinergic signalling in serotonin neuromodulation

Authors: *C. A. WOTTON, L. K. BEKAR
Pharmacol., Univ. of Saskatchewan, Saskatoon, SK, Canada

Abstract: It is well established that serotonin (5HT) plays a critical role in shaping cortical network activity by affecting inhibition. However, we call in to question the mechanism through which this is thought to occur. Previous literature claims that 5HT is having its effects via direct action on interneurons. While this may occur, limitations in neuromodulator diffusion, such as degradation and uptake, would limit the ability of 5HT to have rapid actions on these inhibitory networks. We propose that astrocytes, which possess 5HT receptors, the means to influence inhibitory networks via purinergic signaling, and are each in contact with over 100,000 synapses are the ideal intermediary to aid 5HT in rapidly modulating cortical inhibition. In addition, 5HT has the ability to alter cellular metabolism which may occur in astrocytes and result in release of purinergic gliotransmitters. Previous results indicate 5HT is affecting cortical inhibition via purinergic and GABAergic mechanisms. This study sought to narrow down those mechanisms and establish a role for astrocytes in the 5HT effects on inhibition. We used both whole-cell patch-clamp technique (neurons/astrocytes) and extracellular field recordings in acutely isolated mouse brain slices. A paired-pulse paradigm was used in field recordings to indirectly assess

whole network changes in inhibition, while whole-cell recordings allowed for direct observation of changes in inhibitory currents. Results thus far indicate that adenosine A2A and ATP P2Y receptors, which are both previously established to depolarize interneurons, are playing a role in the 5HT effect on cortical networks. In patch recordings, we see that antagonists at the P2Y and A2A receptors block the 5HT increase in spontaneous inhibitory currents. Alternatively, using agonists at these same receptors produces an effect similar on inhibition to 5HT in field recordings. Finally, a known antagonist of astrocyte metabolism, iodoacetate, was also found to attenuate 5HT effects on inhibition in both field and patch recordings. These results suggest the importance of the largely unacknowledged existence of astrocytic output in aiding neuromodulatory shaping of the flow of information in the cortex.

Disclosures: C.A. Wotton: None. **L.K. Bekar:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.04/L2

Topic: B.11. Glial Mechanisms

Support: Deutsche Frauenhofe Gesellschaft SFB 1134

Title: Astroglial activity during gamma oscillations in acute hippocampal slices

Authors: *H. JAKOBI[1], T. HONDRICH[1], P. GESCHWILL[2], J. SCHNEIDER[3], E. KIRSCHBAUM[4], F. HAMPRECHT[4], O. KANN[3], M. BOTH[2], R. SPRENGEL[1]
[1]Max Planck Res. Group of Dr. Rolf Sprengel, Heidelberg, Germany; [2]Inst. of Physiol. and Pathophysiology, University Heidelberg, Germany; [3]Gen. Neurophysiol., Inst. of Physiol. and Pathophysiology, Heidelberg University, Germany; [4]Heidelberg Collaboratory for Image Processing, University Heidelberg, Germany

Abstract: Gamma oscillations and sharp wave ripples complexes (SWR) in the hippocampus are thought to be associated with memory acquisition and consolidation during slow wave sleep. Both these oscillatory neuronal activities can be measured *in vivo* and in hippocampal slice preparations. Since recent studies measuring Ca^{2+} activity in astrocytes suggested a relay function of astrocytes on activity states of large neuronal circuits and since the existence of the bi-directional astrocyte-to-neuron communication is well documented, we analyzed a potential role of astrocyte activity and SWR and gamma oscillations in acute ventral hippocampal slices and hippocampal slice cultures. Therefore, we simultaneously monitored SWR with a multi-electrode array and astrocytic Ca^{2+} transients with confocal microscopy in acute hippocampal slices, infected with GCaMP6f-expressing recombinant adeno-associated virus (rAAV). In six slices of two rAAV injected C57BL/6 mice we could not detect any correlation between the

occurrence of SWR and astrocyte Ca^{2+} signaling. In another approach we measured astrocyte Ca^{2+} signals after gamma oscillation induction in hippocampal slice cultures. Here we observed in 10 slices, a statistically significant increase in total astrocyte Ca^{2+} activity upon onset of gamma oscillation.
Conclusion: Our results show that astrocytes respond to the induction of gamma oscillations in hippocampal slice culture but show no specific Ca^{2+} response when SWR are observed in acute hippocampal slice. It remains to be elucidated if astrocytes follow the neurons in their activity increase, lead or merely independently accompany the neurons during the onset of gamma oscillations. This work was supported by the German Research Foundation (SFB1134).

Disclosures: H. Jakobi: None. **T. Hondrich:** None. **P. Geschwill:** None. **J. Schneider:** None. **E. Kirschbaum:** None. **F. Hamprecht:** None. **O. Kann:** None. **M. Both:** None. **R. Sprengel:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.05/L3

Topic: B.11. Glial Mechanisms

Support: FISM grant 2012/R/2
NIH NINDS Grant NS-084303-01A1
The Miami Project To Cure Paralysis
FISM grant 2015/R/7

Title: Role of astroglial TNFR2 in cognition, memory and anxiety

Authors: *P. ILLIANO[1], H. DESU[1], M. PLASTINI[1], S. MUDALEGUNDI[1], M. M. MOOSA[1], M. KARJANMAA[2], R. BRAMBILLA[3]
[1]Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL; [2]Univ. of Southern Denmark, Odense, Denmark; [3]The Miami Project To Cure Paralysis, Dept. of Neurosurg., Univ. of Miami Miller Sch. of Med., Miami, FL

Abstract: Tumor necrosis factor (TNF) is a pleiotropic cytokine implicated in key physiologic and pathologic processes in the central nervous system (CNS). These range from modulating synaptic plasticity, thereby regulating memory and cognitive function, to participating in the pathophysiology of neurologic disorders such as multiple sclerosis, Alzheimer's disease, stroke, etc. TNF exists in two forms, transmembrane (tmTNF) and soluble (solTNF), whose functions are mediated by TNFR1 and TNFR2. The signals activated by the two receptors are often opposite: TNFR1 mediates apoptosis and inflammation, while TNFR2 mediates cell survival, immunity and myelination. Studies with knockout mice have implicated TNFR2 in the regulation

of cognitive function in non-inflammatory physiological conditions. However, the cell type that contributes to this effect is still unknown. Given that astrocytes are key players in synaptic function and they express TNFR2, we sought to investigate whether astroglial TNFR2 could be implicated in regulating cognition and memory. To do so, we generated conditional knockout mice to selectively ablate TNFR2 in GFAP expressing astrocytes (GFAPcre^{ERT2}:Tnfrsf1b$^{fl/fl}$ mice). We found that astroglial TNFR2 ablation impairs memory and cognition, measured with the novel object recognition test, and spatial memory recognition, measured with the Morris water maze test. Ablation of TNFR2 in astrocytes also resulted in anxiety-like behaviors determined with the light-dark transition test. Furthermore, GFAPcre^{ERT2}:Tnfrsf1b$^{fl/fl}$ mice displayed astrogliosis and microgliosis in the hippocampus, shown by increased numbers of GFAP^{+} and Iba1^{+} cells. Taken together our data point at a role for astroglial TNFR2 in cognition, memory and anxiety, as well as hippocampal homeostasis. Further studies are warranted to better understand the mechanisms of these effects, and whether they are maintained under CNS disease conditions.

Disclosures: P. Illiano: None. **H. Desu:** None. **M. Plastini:** None. **S. Mudalegundi:** None. **M.M. Moosa:** None. **M. Karjanmaa:** None. **R. Brambilla:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.06/L4

Topic: B.11. Glial Mechanisms

Support: F31NS089178
T32NS043124
F31NS092435
R01NS078294
U54HD083092
McNair Medicine Institute
Charif Souki Fund

Title: Olfactory bulb astrocytes modulate activity-dependent sensory processing and map refinement

Authors: *K. UNG[1], B. R. ARENKIEL[2], B. TEPE[3], E. HANSON[4], C. K. MCCLARD[3], G. LIU[3], B. DENEEN[3]
[1]Developmental Biol., [2]Mol. & Human Genetis and Neurosci., [4]Neurosci., [3]Baylor Col. of Med., Houston, TX

Abstract: Despite important roles astrocytes play in synaptic plasticity, how astrocytes function towards processing sensory information remains largely unexplored. Exploiting the anatomy and experimental tractability of the mouse olfactory system, here we test the hypothesis that local astrocytes play essential roles in sensory circuit processing, and the maintenance of odor response maps in the olfactory bulb. By genetically targeting both astrocytes and neurons for simultaneous *in vivo* imaging of Ca^{2+} responses, we found that astrocytes exhibited an odor-response map that overlapped with excitatory neuronal activity. Furthermore, we observed that stimulating or inhibiting astrocyte intracellular Ca^{2+} signaling inversely modulated odor-evoked neuronal activity, suggesting that activation of olfactory bulb astrocytes inhibits neuronal odor responses. Moreover, this inhibitory effect was mediated by calcium-dependent vesicular release, and was critical in maintaining neuronal sensory domains. Finally, behavioral analysis showed that astrocyte activity manipulations affected both odor detection threshold and olfactory discrimination, supporting an active role for astrocytes in information processing within olfactory sensory circuits. Together, these data support functional roles astrocytes play in sensory processing, highlighting a dynamic neuron-glia mechanism to sculpt and maintain sensory maps. Uncovering novel functional roles for astrocytes toward sensory processing and circuit function may not only better inform us of proper brain development, but may also help explain how defects in astrocytes contribute to brain circuit dysfunction or disease.

Disclosures: K. Ung: None. **B.R. Arenkiel:** None. **B. Tepe:** None. **E. Hanson:** None. **C.K. McClard:** None. **G. Liu:** None. **B. Deneen:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.07/L5

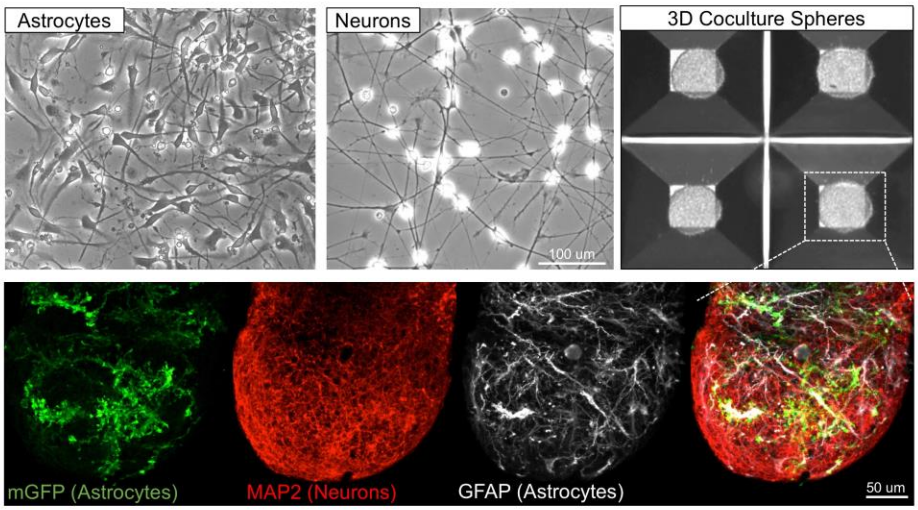
Topic: B.11. Glial Mechanisms

Title: Investigating neuron-astrocyte functional interactions using a bioengineered 3D coculture platform

Authors: *C. CVETKOVIC, N. BASU, R. KRENCIK
Houston Methodist Res. Inst., Houston, TX

Abstract: The manner in which human astrocytes respond and contribute to developing neuronal circuits is not widely understood. It especially remains unclear how their response is altered during neuromodulation approaches such as drug intervention or electrical stimulation (ES). We hypothesize that enhancement of neuronal activity in turn stimulates astrocytes to secrete neuroregenerative factors previously identified[1]. We aim to utilize this knowledge in future preclinical studies to test whether regulation of astrocyte extracellular signaling can promote neuroregeneration after injury and disease.

Human astrocytes have distinct morphological and functional attributes which may lead to dissimilar responses from non-human cellular models; as such, we utilize tissue generated from human pluripotent stem cells. We also sought to recapitulate the complexity of human astrocytes and their intimate synaptic associations with improved culture conditions. Thus, we devised an efficient method to systematically and rapidly bioengineer 3D coculture spheres containing human neurons and astrocytes using organoid technologies[2] (*Fig 1*). To modulate neuronal activity, we introduced direct ES of 100Hz with 10 mV square wave pulses, then assessed how coculture and enhanced neural activity affected cellular maturation with gene expression profiling, immunohistochemistry and multielectrode array recordings. We found that the presence of astrocytes accelerated neuronal circuit formation, while neuronal stimulation led to dramatic morphological changes in astrocytes. Surprisingly, astrocytes respond directly to ES suggesting there may be a combination of neuronal signals and cell autonomous results.
In summary, we report an optimized coculture system to stimulate and measure the responses of neuron-astrocyte signaling and are conducting further characterization to elucidate the specific signaling factors involved. As a preclinical platform, this system may be effective to define the impact of ES on astrocyte signaling. (Krencik et al, [1]*Sci Transl Med* 2015; [2]*Stem Cell Rep* 2017)



Disclosures: C. Cvetkovic: None. **N. Basu:** None. **R. Krencik:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.08/L6

Topic: B.11. Glial Mechanisms

Support: NINDS R01 NS089791

Title: Developmental analysis of astrocytes and astrocyte-derived synapse promoting proteins in the mouse visual cortex *in vivo*

Authors: *I. FARHY TSELNICKER, C. DOWLING, N. J. ALLEN
The Salk Inst. For Biol. Studies, LA Jolla, CA

Abstract: Astrocytes, a major type of glial cells, are crucial regulators of neuronal synapse development and function. In the rodent cortex neurons are arranged in 6 layers, each with stereotyped synaptic connectivity between layers and with neurons outside the cortex. The correct establishment of these synapses during development is crucial for the proper function of the brain. Astrocytes produce several proteins that promote synapse formation and function, however, whether cortical astrocytes differentially regulate formation of synapses in different layers is unknown. Furthermore, the developmental time line of expression of astrocyte synaptogenic cues in the different cortical layers, and whether expression is regulated by neuronal activity, is unknown. Here we use mouse visual cortex to study the development of astrocytes, astrocyte-derived synapse promoting proteins glypicans and thrombospondins, and neuronal synaptic proteins Vesicular Glutamate transporters (VGlut1, 2) and AMPA receptor subunits GluA1, 2. We perform our analysis at 4 different stages of cortical astrocyte and synapse development: 1) Postnatal day (P) 0-4: astrocytes are at early stages of generation and proliferation; synapses have not yet formed, 2) P7 - astrocytes are immature, continue to proliferate; synapses begin to form, 3) P14 - peak of synaptogenesis, beginning of synapse maturation 4) P21-P28 end of synaptogenesis; astrocytes and synapses are mature. Through a combination of immunohistochemistry and in situ hybridization methods we quantify the developmental changes in astrocyte numbers within each of the 6 neuronal layers, and ask whether the expression of astrocyte-derived synapse-promoting genes is segregated by layers, and how their expression patterns and localization change with development. Furthermore, we ask whether perturbing development of thalamo-cortical innervation of the visual cortex alters the expression levels and/or localization of astrocyte-derived synapse promoting factors. Our findings constitute an important frame work for future studies of astrocyte and synapse development in the cortex, as well as provide insight into neuron-astrocyte interaction as it occurs at the level of the distinct cortical connections during synapse development.

Disclosures: I. Farhy Tselnicker: None. **C. Dowling:** None. **N.J. Allen:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.09/L7

Topic: B.11. Glial Mechanisms

Support: DA035088

Title: The neuropeptide PACAP orchestrates glutamate signaling between astrocytes and neurons in the nucleus accumbens core: implications for cocaine seeking

Authors: *E. M. HESS[1], S. KASSEL[1], L. KONG[4], N. RADDATZ[1], E. VAN NEWENHIZEN[2], E. AFREEN[1], E. BARDONNER[1], D. KORPICS[1], Q.-S. LIU[5], A. GEURTS[6], J. R. MANTSCH[1], S. CHOI[3], D. A. BAKER[3]
[2]Biomed. Sci., [3]Dept Biomed. Sci., [1]Marquette Univ., Milwaukee, WI; [4]Waisman Ctr., Univ. of Wisconsin-Madison, Madison, WI; [5]Dept. of Pharmacol. and Toxicology, [6]Physiol., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Dysregulation of glutamate signaling is observed in humans abusing cocaine, opiates, and other drugs. A challenge in revealing the glutamatergic basis of addiction is that it signals via an elaborate network of receptors, transporters, and release mechanisms expressed by neurons and astrocytes. Preclinical studies have revealed that cocaine dysregulation of glutamate signaling stems from disrupted function of neurons and astrocytes. Glutamate signaling across these cells is likely to be highly coordinated. In support, cocaine, which targets neuronal monoamine transporters, impairs the astrocytic cystine-glutamate antiporter system x_c^- (Sxc) in the nucleus accumbens core (NAcc). Hence, the NAcc may contain an unidentified molecule capable of coordinating glutamate signaling across neurons and astrocytes. Here, we hypothesize that the neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) is a previously unrecognized component of glutamate signaling in the NAcc that integrates signaling between neurons and astrocytes. To test this, we used adult male rats to examine whether PACAP and PACAP receptors are expressed in the NAcc. To do this, we fluorescently labelled NAcc afferents, efferents, and astrocytes. Subsequently, the use of fluorescence activated cell sorting followed by PCR enabled the detection of PACAP mRNA in NAcc afferents and PACAP receptor mRNA in NAcc efferents and astrocytes. Regarding the role of PACAP signaling in astrocytes, we found that PACAP decreased the apparent K_m of Sxc-mediated cystine-glutamate exchange. In neurons, PACAP signaling was found to promote NMDA receptor activation, an effect that may be due to altered phosphorylation of the GluN1 subunit at S897. The net impact of promoting glutamate release from astrocytes and regulating neuronal NMDA receptors was inhibition of AMPA receptor function in NAcc efferents to the substantia nigra. The relevance of these findings to drug addiction was established by our finding that PACAP micro-injections into the NAcc dose-dependently reduced cocaine-primed reinstatement of extinguished cocaine seeking. Moreover, micro-injection of a PACAP receptor antagonist promoted cocaine-primed reinstatement, which indicates that this neuropeptide may be an endogenous factor protecting against compulsive drug seeking. These findings suggest that the neuronal factor PACAP is a key integrator of the glutamate network in the NAcc that enables a neuron-astrocyte signaling pathway promoting control over drug-induced behavior.

Disclosures: E.M. Hess: None. **S. Kassel:** None. **L. Kong:** None. **N. Raddatz:** None. **E. Van Newenhizen:** None. **E. Afreen:** None. **E. Bardonner:** None. **D. Korpics:** None. **Q. Liu:** None. **A. Geurts:** None. **J.R. Mantsch:** None. **S. Choi:** None. **D.A. Baker:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.10/L8

Topic: B.11. Glial Mechanisms

Title: A neuron-glia co-culture model system to study neuroinflammation

Authors: *N. M. TAYLOR, S. HAKIM, A. BHATTACHARYA, Y. HE
Janssen, San Diego, CA

Abstract: Astrocytes and microglia are major glial cell types in the brain and play fundamental roles in association with neuronal networks in the central nervous system. Inflammation or dysfunction of either contribute to neurologically associated disorders and diseases. To investigate the involvement of astrocytes and microglia in health and diseases and identify potential therapeutic targets, it is critical to establish reliable isolation methods for individual cell types as well as co-culture glial-neuronal systems. Here we explored neuronal, microglial, and astrocyte purification and co-culture methods. Furthermore, we assessed the effects of glia and LPS-stimulated glia on neurite length and neuronal activity. As a result, we found: 1) a method to obtain pure neurons; 2) Brainbits media maintained microglia in a relatively quiescent state; 3) neurite length was suppressed by LPS-induced microglia but not LPS-induced astrocytes; 4) neuronal activity was enhanced by astrocyte co-culture. Our study provides a useful tool as a co-culture system to mimic the *in vivo* brain environment, which can be applied for further compound testing and mechanism studies.

Disclosures: N.M. Taylor: A. Employment/Salary (full or part-time):; Janssen Research & Development LLC. **S. Hakim:** None. **A. Bhattacharya:** None. **Y. He:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.11/L9

Topic: B.11. Glial Mechanisms

Title: An astrocyte-neurons model of emergent spatial modulation of synapses mediated by endocannabinoid

Authors: Y. NAKAHAMA, *O. ARAKI, T. URAKAWA
Tokyo Univ. of Sci., Tokyo, Japan

Abstract: We focused on the interactions between an astrocyte and neurons through endocannabinoid (ECB). ECB transmitted retrogradely from an active postsynaptic neuron to presynaptic neurons has been reported to decrease the probability of release (PR) of neurotransmitter at synaptic cleft. This inhibitory effect is called Depolarization-induced Suppression of Excitation (DSE). On the other hand, when a microdomain of astrocyte also receives the ECB, the inositol trisphosphate (IP_3) is generated in the astrocyte. Then, calcium waves induced by IP_3 increase PR by glutamate release from the astrocyte. This phenomenon is referred to as endocannabinoid-mediate Synaptic Potentiate (e-SP). Further, it has been reported that DSE occurs in the shorter range of distance (< 60 μm) from the electrically stimulated cell, while e-SP occurs at the longer range of distance (Navarrete et al., 2010). The mechanism underlying this distance dependency remains unclear. Using a computational model, we attempted to verify the hypothesis that ECB release and IP_3 diffusion in astrocyte play an important role in such spatial modulation of synapses. Our model consists of three parts as follows: (Part 1) membrane potentials of neurons, (Part 2) intracellular calcium wave with IP_3 in an astrocyte (Li-Rinzel, 1994, De Pitta et al., 2009), and (Part 3) ECB release among the astrocyte and neurons (Naeem et al., 2015). We used the adaptive exponential integrate-and fire model (Destexhe, 2009) as a model neuron. Part 2 of our model was set to make the dynamics of Ca^{2+} stored in endoplasmic reticulum (ER) and its release from ER, which depend on IP_3 concentration. We assumed 100 x 100 neurons arranged on the grid points in a 2D plane and one astrocyte interacting with all of them. When one neuron fires, it releases ECB around it. Then, DSE occurs in the presynaptic neurons which receive the ECB. On the other hand, if the astrocyte receives ECB, IP_3 is generated. If $[Ca^{2+}]$ exceeds a threshold depending on IP_3 concentration, e-SP occurs. Here, we uniquely introduced the spatial IP_3 diffusion model which follows a diffusion equation in the astrocyte aiming for the distance-dependent DSE and e-SP. Our computational simulation showed a circular area of decreased PR within about 30 μm from the stimulated neurons and increased one from there to 150 μm apart. The results were almost consistent with the actual experimental data (Navarrete et al., 2010). In addition, no distance-dependent modulation was observed without IP_3 diffusion. The present results support our hypothesis that IP_3 diffusion in astrocyte is involved in spatial modulation of synapses.

Disclosures: Y. Nakahama: None. **O. Araki:** None. **T. Urakawa:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.12/L10

Topic: B.11. Glial Mechanisms

Support: Brain Research Foundation Fay/Frank Seed Grant
Citizens United for Research in Epilepsy (CURE) Taking Flight Award
Beckman Institute Postdoctoral Fellowship
Beckman Institute Undergraduate Fellowship

Title: Optogenetic stimulation of astrocytic Gq signaling differentially alters synaptic transmission in hippocampal CA1 and layer V of sensorimotor cortex

Authors: *C. SOBIESKI[1,2,3], N. M. WOJNOWSKI[2,3], C. RAMAKRISHNAN[4], R. A. DEFAZIO[5], K. DEISSEROTH[4], C. A. CHRISTIAN[2,3]
[2]Beckman Inst., [3]Dept. of Mol. and Integrative Physiol., [1]Univ. of Illinois Urbana-Champaign, Urbana, IL; [4]Dept. of Bioengineering, Stanford Univ. Dept. of Psychology, Stanford, CA; [5]Mol. and Integrative Physiol., Univ. of Michigan, Ann Arbor, MI

Abstract: Appreciation of active roles for astrocytes in shaping central nervous system function is growing. While astrocytes can detect synaptic signaling through G-protein linked receptors, the subsequent effects of this response on synaptic function are less understood. It is also unclear how these effects may differ across brain areas. These questions have been difficult to address due to limited availability of tools that selectively activate G-protein signaling pathways in astrocytes. Here we investigated how the activation of Gq signaling in astrocytes modulates synaptic transmission in hippocampal CA1 and layer V of sensorimotor cortex. C57BL/6J mice were injected with adeno-associated virus (AAV8) to express either a light-sensitive Gq-linked alpha1 adrenergic receptor and GFP (optoa1) or control GFP alone under the astrocyte promoter GFAP. Successful targeting of opsin/GFP to astrocytes was confirmed by histology. At least two months after virus injection, we used whole-cell patch clamp electrophysiology in acute brain slices to measure spontaneous inhibitory postsynaptic currents (sIPSCs) or excitatory postsynaptic currents (sEPSCs) while delivering 1 mW, 5 mW, or 10 mW blue laser light (473 nm) to the slice via an optical fiber at 0.5 Hz for 90 s. Biocytin filling of recorded cells confirmed localization near GFP-expressing astrocytes. While there was little effect on sPSC kinetics at 1 mW and 5 mW light intensities for either optoa1 or GFP-expressing slices, in hippocampal CA1 pyramidal cells we found that sIPSC decay time was increased when optoa1 was stimulated at 10 mW compared to baseline recordings (N=8 cells, $p<0.0001$, K-S test). We did not observe this effect in GFAP-GFP controls (N=10 cells GFP; $p=0.1150$, K-S test). We also found that light pulses increased sEPSC amplitude in GFP controls (N=10 cells; $p<0.0001$, K-S test), but not in slices expressing optoa1 (N=9 cells; $p=0.1845$, K-S test). Compared to CA1, preliminary results from pyramidal neurons in layer V sensorimotor cortex show decreased sIPSC decay time following optoa1 stimulation (N= 5 cells; $p=0.0048$, K-S test). These initial data suggest that acute activation of Gq G-protein signaling in astrocytes has differential effects on sIPSC kinetics in hippocampus vs. cortex.

Disclosures: C. Sobieski: None. **N.M. Wojnowski:** None. **C. Ramakrishnan:** None. **R.A. DeFazio:** None. **K. Deisseroth:** None. **C.A. Christian:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.13/L11

Topic: B.11. Glial Mechanisms

Support: NIH RO1 HL128454.

Title: Astrocytic excitatory amino acid transporters (EAATs) differentially regulate metabotropic glutamate receptor (mglur) activation in normoxia and chronic intermittent hypoxia (CIH)

Authors: *D. MARTINEZ, E. M. HASSER, D. D. KLINE
Biomed. Sciences/Dalton Cardiovasc. Res. Ctr., Univ. of Missouri, Columbia, MO

Abstract: The nucleus tractus solitarii (nTS) is the first central integration site for visceral reflexes including the chemoafferent reflex. Sensory afferent signals are transmitted to nTS neurons via release of Glutamate (Glu). EAATs in the nTS restrain extracellular Glu, ionotropic Glu receptor activation, and thus modulate neuronal activity and synaptic transmission. We have shown that EAAT block (EAAT-X) with the general antagonist DL-threo-β-Benzyloxyaspartic acid (DL-TBOA) depolarized nTS neurons and increased the frequency of spontaneous excitatory postsynaptic currents (sEPSC); yet reduced the amplitude of afferent (TS)-evoked EPSCs (TS-EPSCs). Interestingly, CIH, a model of obstructive sleep apnea, produces similar synaptic and neuronal responses as EAAT-X. EAATs in the nTS may modulate synaptic and neuronal excitability via mGluR activation, as iGluR blockers did not fully eliminate EAAT-X effects. Group I mGluRs are found on nTS neuron somas; their activation leads to depolarization and increased excitability. Group II/III are found presynaptically; their activation decreases TS-EPSC amplitude. We sought to determine the influence of EAATs on a) CIH-induced changes, and b) mGluRs in CIH responses. Male Sprague-Dawley rats (3-6 wk) underwent 10d normoxia (Norm, 21% O_2) or 10d CIH (alternating 21% O_2 and 6% O_2, 8h/day). Horizontal brainstem nTS slices were generated and sEPSCs, TS-EPSCs, and holding currents (I_{hold}), were recorded from monosynaptic nTS neurons. Electrophysiological properties were examined in aCSF, EAAT-X (TFB-TBOA, 500 nM) alone, and during EAAT-X and block of either Grp I (LY367385 160 μM) or Grp II/III (eGLU and MSOP 200 μM). As a time control, some neurons were exposed to a second EAAT-X (EAAT-X2). In Norm, EAAT-X increased both I_{hold} (depolarized V_m) and sEPSC frequency (indicating an increase in network activity), yet decreased the amplitude of TS-EPSCs. EAAT-X2 enhanced all of these effects. mGluR-I-X eliminated the enhancement of I_{hold} and sEPSC frequency seen with EAAT-X2. Conversely, mGluR-II/III-X attenuated TS-EPSC depression seen in EAAT-X2. In CIH, EAAT-X increased I_{hold} and sEPSC frequency but less than in Norm. CIH decreased TS-EPSC amplitude compared to NORM, yet EAAT-X increased

TS-EPSC amplitude. EAAT-X2 enhanced these effects. In contrast to Norm, mGluR-I-X further increased sEPSC frequency and I_{hold} to EAAT-X2. mGluR-II/III-X decreased the TS-EPSC amplitude to EAAT-X2. These data suggest in Norm that EAATs regulate network activity and I_{hold} through mGluR I, and TS-EPSCs through mGluR II/III. CIH reduces EAAT influence on synaptic and neuronal activity, and mGluRs contribute differentially.

Disclosures: D. Martinez: None. **E.M. Hasser:** None. **D.D. Kline:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.14/L12

Topic: B.11. Glial Mechanisms

Support: NIH NINDS Grant R01NS082570

Title: Astrocyte volume changes associated with cortical seizures *in vivo*

Authors: *T. R. MURPHY[1], T. A. FIACCO[2], D. K. BINDER[1]
[1]Div. of Biomed. Sciences, Sch. of Med., [2]Dept. of Molecular, Cell and Systems Biol., Univ. of California, Riverside, Riverside, CA

Abstract: Epilepsy is a large spectrum of recurrent seizure disorders which collectively afflict over 65 million people worldwide. The mechanisms underlying seizure generation remain largely unknown, and current therapies which target neurons alone often fail to control seizures. More specific targets require a more fundamental understanding of the factors driving neuronal hyperexcitability and seizure susceptibility. One intriguing, often-overlooked factor in neuronal excitability is the size of the extracellular space (ECS). ECS shrinkage (reflecting cell/tissue swelling) has been repeatedly demonstrated to augment tissue excitability and seizure susceptibility, and seizures in multiple models are preceded by ECS reductions. Conversely, a dilated ECS (cell/tissue shrinking) produces the opposite effect. ECS volume changes likely reflect those of astrocytes, which facilitate brain water movements and rapidly change volume under osmotic gradients and facilitate brain water movement through aquaporin-4 (AQP4) water channels. Swollen astrocytes can also volume regulate under certain conditions, releasing neurotransmitters in the process and potentially further increasing neuronal excitability. We have previously observed rapid astrocyte swelling prior to excitability increases in hippocampal slices, and preliminary work indicates that reactive astrocytes in epileptic mice are even more susceptible to swelling. To date, however, the exact relationship between astrocyte volume change and neuronal excitability *in vivo* remains unknown. Using *in vivo* two-photon imaging alongside cortical EEG recording, we have begun to directly examine the temporal relationship between astrocyte volume changes and cortical seizures in awake, behaving animals. Rapid

(1/minute) z-stack images of layer 2/3 cortical astrocytes were acquired continuously before, during and after acute generalized seizure (induced by pentylenetetrazole) in Aldh1L1-eGFP mice to obtain astrocyte volume measurements over time. In agreement with previous findings, we have observed rapid astrocyte swelling occurring minutes before seizure initiation, reaching a peak of nearly 8% above baseline volume, before dropping precipitously just prior to seizure. Preliminary results indicate that GFP-expressing neurons do not show similar volume changes. These data suggest that astrocyte volume changes may specifically promote seizure initiation. Ongoing experiments include the use of a focal (4-aminopyridine) seizure model and specific manipulations of astrocyte volume to more specifically determine the influence of astrocyte swelling on hyperexcitability.

Disclosures: T.R. Murphy: None. **T.A. Fiacco:** None. **D.K. Binder:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.15/L13

Topic: B.11. Glial Mechanisms

Support: RO1MH067121

Title: Regulation of excitatory and inhibitory synapses through astrocytic ephrin-B1 in developing and adult hippocampus

Authors: *A. Q. NGUYEN[1], J. KOEPPEN[1], S. HANNA[1], A. VENGALA[1], A. OBENAUS[3], I. M. ETHELL[2]
[2]Sch. of Med., [1]Univ. of California, Riverside, Riverside, CA; [3]Dept Pediatrics, Loma Linda Univ., Loma Linda, CA

Abstract: Synapses undergo structural and functional modifications during development, which is regulated by astrocytes. Astrocyte dysfunctions are also implicated in synapse pathologies associated with neurodevelopmental disorders such as autism and intellectual disabilities. Astrocytes can regulate both formation and elimination of functional synapses during development. In addition, astrocytes can regulate synapse maintenance and plasticity in the adult brain. We propose that astrocytic ephrin-B1 may negatively influence synapse growth by mediating pruning of existing synapses or suppressing new synapse formation through the interactions with neuronal EphB receptors. To test this hypothesis, we first examined whether the deletion of astrocytic ephrin-B1 during early postnatal development (P14→P28) or in adulthood (P90) would result in excessive formation of synapses in the hippocampus. Deletion was achieved using ERT2-Cre^{GFAP}*ephrin-B1*$^{flox/y}$ mouse model; P14 or adult *ephrin-B1*$^{flox/y}$ (WT) and Cre^{GFAP}*ephrin-B1*$^{flox/y}$ (KO) male littermates were intraperitoneally injected with tamoxifen

(0.5mg in 5mg/ml of 1:9 ethanol/sunflower seed oil) once a day for 5 or 7 days, and analyzed 2 weeks after first tamoxifen injection. Astrocytic ephrin-B1 deletion in adult male mice resulted in significant increase in dendritic spine density and pre-synaptic vGlut1 puncta with no changes to GAD65 puncta in stratum radiatum (SR) of CA1 hippocampus. Interestingly, we found an increased proportion of immature dendritic spines with small heads along with a two-fold decrease in synaptic AMPAR levels. We also observed an overall decrease in postsynaptic firing of CA1 hippocampal neurons in KO mice following stimulation of Schaffer Collaterals. In contrast, early postnatal deletion of astrocytic ephrin-B1 resulted in significantly increased postsynaptic fEPSPs and postsynaptic firing of CA1 hippocampal neurons. Our results suggest that astrocytic ephrin-B1 may regulate the development of hippocampal circuits by suppressing excitatory synapse formation or by influencing excitatory-inhibitory balance.

Disclosures: A.Q. Nguyen: None. **J. Koeppen:** None. **S. Hanna:** None. **A. Vengala:** None. **A. Obenaus:** None. **I.M. Ethell:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.16/L14

Topic: B.11. Glial Mechanisms

Title: Noradrenergic enhancement of antidepressant-induced LPA_1 signalling in astrocytes

Authors: *P. ONALI, S. DEDONI, M. C. OLIANAS
Univ. of Cagliari, Dept.Biomedical Sci., Monserrato, Italy

Abstract: Antidepressants are considered to exert their therapeutic effects by enhancing monoaminergic neurotransmission. However, there is evidence that these drugs have additional molecular targets, including G protein-coupled receptors. We have recently shown that in different cell types distinct classes of antidepressants activate the lysophosphatidic acid (LPA) receptor LPA_1. In cultured astrocytes antidepressant-induced LPA_1 activation triggers growth factor receptor transactivation, ERK1/2 phosphorylation and protection from oxidative stress. However, it is not known whether in astrocytes monoamines can affect antidepressant-induced LPA_1 signalling. We found that in C6 glioma cells and in cultured rat cortical astrocytes prolonged exposure to either noradrenaline or the selective β-adrenergic agonist l-isoproterenol enhanced the stimulation of ERK1/2 phosphorylation elicited by either amitriptyline, mianserin or LPA. The noradrenergic potentiation was mimicked by the adenylyl cyclase stimulator forskolin, the cyclic AMP analogue dibutyryl-cAMP and PDE4 inhibitor rolipram, implying the involvement of a cyclic AMP-dependent mechanism. These data suggest that the enhancement of β-adrenergic transmission elicited by certain antidepressants may potentiate the action of these drugs as stimulators of LPA_1-mediated signalling in astrocytes.

Disclosures: P. Onali: None. **S. Dedoni:** None. **M.C. Olianas:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.17/L15

Topic: B.11. Glial Mechanisms

Support: NIH IRP
Wellcome Trust

Title: Optogenetic manipulation of preBötzinger complex astrocytes modulates activity of inspiratory rhythm-generation circuits

Authors: *S. SHEIKHBAHAEI[1,2], H. KOIZUMI[1], R. ZHANG[1], A. V. GOURINE[2], J. C. SMITH[1]
[1]Cell. and Systems Neurobio. Section, Natl. Inst. of Hlth. (NIH)- NINDS, Bethesda, MD; [2]Univ. Col. London, London, United Kingdom

Abstract: Astrocytes, the electrically silent CNS cells, have been proposed to modulate neuronal network activity, including vital brainstem respiratory rhythm-generating circuits of the preBötzinger complex (preBötC), although such a modulatory function at the level of preBötC circuits has not been directly demonstrated. We employed transgenic mice expressing Cre recombinase under control of the human glial fibrillary acidic protein (hGFAP-cre) promoter for astrocyte-specific expression of Channelrhodopsin-2 (ChR2) or archaerhodopsin (ArchT) and applied optogenetic techniques to manipulate activation of preBötC astrocytes in rhythmically active neonatal medullary slice (*in vitro*) and in adult perfused brainstem-spinal cord preparations (*in situ*). Activation of ArchT in preBötC astrocytes via laser (593 nm, 2-10 mW, *in vitro*), decreased the frequency and amplitude of hypoglossal nerve activity, while laser activation of ChR2 (473 nm, 0.5-5 mW) in preBötC astrocytes increased the frequency of hypoglossal (*in vitro*) and phrenic nerve (*in situ*) activities. Our experimental results have confirmed the capability of astrocytes to modulate the activity of preBötC rhythm-generating circuits. Identifying the astrocytic signaling mechanisms involved remains an important problem.

Disclosures: S. Sheikhbahaei: None. **H. Koizumi:** None. **R. Zhang:** None. **A.V. Gourine:** None. **J.C. Smith:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.18/L16

Topic: B.11. Glial Mechanisms

Support: Bonderman gift grant
National Eye Institute (P30-026877)
Research to Prevent Blindness, Inc.

Title: Increased endoplasmic reticulum stress and gliosis in a model of high altitude retinopathy and CNS hypoxia

Authors: *L. A. MESENTIER-LOURO, A. CAMARGO, V. KUMAR, M. A. SHARIATI, R. DALAL, A. J. OH, Y. J. LIAO
Dept. of Ophthalmology, Stanford Univ., Palo Alto, CA

Abstract: Vision and CNS changes are well described after acute high-altitude exposure, sometimes also called high altitude cerebral edema (HACE) or high-altitude retinopathy. This is primarily attributed to hypoxia as a result of hypobaria. Hypoxia leads to rapid energy failure, cessation of oxidative phosphorylation, and cell death, likely via intrinsic or extrinsic mechanisms. Surprisingly little has been done to study the impact of hypoxia on the retina and optic nerve in the setting of high altitude disease, although hypoxia is thought to be a common mechanism of vision loss in retinopathies and optic neuropathies, including in stroke, glaucoma, ischemic optic neuropathy, diabetic retinopathy, and retinopathy of prematurity. In this study, we used in vivo optical imaging and histology to assess the impact of hypoxia on the retina and optic nerve in a mouse model of acute high-altitude exposure and assessed the impact of treatment with the chemical chaperone 4-phenylbutyric acid (4-PBA).We induced systemic hypoxia in adult (6-8 weeks old) C57BL/6 female mice using a hypoxia chamber, where animals are acclimated over 20 min from 21% oxygen to 6-12% oxygen for 24h or 48h. We performed serial in vivo imaging of the retina using optical coherence tomography, and sacrificed animals at different time points for immunohistochemistry analysis of the retina and optic nerve using antibodies to label different components of the neuron-glia-vascular unit, including C/EBP homologous protein (CHOP; ER stress), Brn3A (retinal ganglion cells), glial fibrillary acidic protein (GFAP; astrocytes and Müller cells), Olig2 (oligodendrocytes) and Iba1 (microglia). To investigate whether ER stress was responsible for hypoxia-induced changes, we treated animals with intraperitoneal injections of 4-PBA (40 mg/kg; ER stress blocker) or vehicle (PBS). Optical coherence tomography showed that hypoxia for 24-48h led to a small but significant reduction in retinal thickness (P=0.0158), which was improved after treatment with 4-PBA. Within 24-48h of hypoxia, we found a profound increase of proapoptotic transcription regulator CHOP, a marker

of ER stress, in the retina (ganglion cell layer and inner nuclear layer) and optic nerve oligodendrocytes. There was also marked gliosis with increased expression of GFAP in the Müller glia, optic nerve head astrocytes and optic nerve astrocytes, and increased $Iba1^+$ microglia in the optic nerve. We showed that CNS hypoxia for 24-48h led to rapid and dramatic activation of ER stress and gliosis in the retina and optic nerve. Reduction of ER stress may be a promising novel treatment for vision changes in high altitude disease and hypoxia.

Disclosures: L.A. Mesentier-Louro: None. **A. Camargo:** None. **V. Kumar:** None. **M.A. Shariati:** None. **R. Dalal:** None. **A.J. Oh:** None. **Y.J. Liao:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.20/L18

Topic: B.11. Glial Mechanisms

Support: SNSF 31003A_143373/1

Title: Astrocytes as orchestrators of long-range synchronization and hippocampal sharp wave ripple generation

Authors: *S. BERRY[1,2], C. LEWIS[1], F. F. VOIGT[1,2], F. HELMCHEN[1,2], U. GERBER[1,2]
[1]Brain Res. Inst., Univ. of Zurich, Zuerich, Switzerland; [2]Neurosci. Ctr. Zurich, Zurich, Switzerland

Abstract: Network oscillations and neuronal synchronization in several brain regions are believed to be key components of memory formation. Traditionally, these processes have been considered the exclusive work of neurons. However, increasing evidence suggests that astroglia can mediate coincident neuronal activity and may even facilitate oscillations in certain brain regions. Here we show that the astrocytic syncytium harbors the ability to synchronize the full hippocampal network, independent of action potentials. Furthermore, we provide *in vitro* and *in vivo* evidence that glia activity is correlated with the generation of sharp wave ripples (SWRs), which are compressed neuronal replay events necessary for memory consolidation. In acute mouse hippocampal slices, we find that the application of K^+ channel antagonists engenders large slow inward currents (SICs) throughout the full neuronal circuit that persist in the presence of tetrodotoxin (TTX). Whole-cell electrophysiological recordings combined with neuronal calcium or glutamate imaging revealed events initiating in CA3c followed by activity in distal CA1 approximately 50 ms later. Astrocytic imaging revealed circuit-wide calcium elevations coincident with neuronal SICs. Manipulations to suppress glial glutamate release inhibited these events. Interestingly, when applied briefly and in the absence of TTX, the K^+ channel antagonists induced persistent SWRs. Considering that this manipulation facilitates both gliotransmission

and SWRs, we explored a potential role for astrocytes as orchestrators of these endogenous hypersynchronous events. Using *in vivo* fiber photometry, we found that astrocytic Ca^{2+} rises are correlated with the occurrence of SWRs in awake mice. Moreover, pharmacological and optogenetic inhibition of gliotransmission abolished endogenous SWRs *in vitro*. Our results reveal novel mechanisms involved in large-scale hippocampal synchronization and the generation of SWRs, indicating that astrocytes may play a previously unappreciated role in memory formation.

Disclosures: S. Berry: None. **C. Lewis:** None. **F.F. Voigt:** None. **F. Helmchen:** None. **U. Gerber:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.21/M1

Topic: B.11. Glial Mechanisms

Support: NIH Grant R01NS094499
NIH Grant R01NS092474
NIH Grant R01NS039444

Title: Myelinated inhibitory axons in mouse and human neocortex

Authors: *K. D. MICHEVA[1], E. F. CHANG[2], A. L. NANA[3], W. W. SEELEY[4], J. T. TING[5], C. COBBS[7], E. LEIN[8], S. J. SMITH[6], R. J. WEINBERG[9], D. V. MADISON[1]
[1]Molec Cell. Physiol, Stanford Univ. Sch. Med., Stanford, CA; [2]Neurosurg., UCSF, San Francisco, CA; [3]Memory and Aging Center, Dept. of Neurol., [4]Memory and Aging Center, Dept. of Neurology, Dept. of Pathology, Univ. of California San Francisco, San Francisco, CA; [5]Human Cell Types, [6]Synapse Biol., Allen Inst. For Brain Sci., Seattle, WA; [7]The Ben and Catherine Ivy Ctr. for Advanced Brain Tumor Treatment, Swedish Neurosci. Inst., Seattle, WA; [8]Human Cell Types, Allen Inst. for Brain Sci., Seattle, WA; [9]Cell Biol. & Physiol., Univ. North Carolina, Chapel Hill, NC

Abstract: Myelinated axons, which account for approximately half the volume of the human brain, are a major factor enabling the dense, rapid, and efficient signal transmission that lies at the heart of human cognitive capacities. The insulating myelin sheath, created by a complex interaction between neuronal and glial cell, keeps axonal impulse propagation velocity high and energy consumption low, while allowing very small overall fiber diameters. Recently, we showed that a large fraction of myelin in mouse neocortex ensheathes axons of inhibitory neurons, specifically of parvalbumin (PV) basket cells (1). These inhibitory myelinated axons differ significantly from the excitatory axons in structural organization (length of nodes of

Ranvier and internodes), and in biochemical composition (axonal cytoskeleton and protein content of myelin). Using samples of surgically-excised brain tissue, we now show that many of the characteristic features of mouse cortical myelinated axons are also present in human, despite 100 million years of evolutionary isolation. As in mouse, many human myelinated inhibitory axons originate from PV interneurons and have distinctive features, including high neurofilament and low microtubule content, short nodes of Ranvier, and high content of myelin basic protein in their myelin sheath. The implications of these differences will require further study, but we speculate that they have direct functional significance. We further show that the inhibitory myelinated axons in both human and mouse cortex have more mitochondria, as well as more 2',3'-cyclic nucleotide 3'-phosphodiesterase, a protein enriched in the myelin cytoplasmic channels thought to provide access for trophic support from ensheathing oligodendrocytes. This is consistent with the high energy demands of fast-spiking PV interneurons and suggests that, in addition to influencing conduction velocity, the myelination of inhibitory axons is likely beneficial for managing their energy consumption by increasing the efficiency of action potential propagation, and providing trophic support. The distinctive features of myelinated inhibitory axons in human cortical grey matter may have important implications for neurological disorders that involve pathologies of myelinated axons. The similarities in structural and biochemical characteristics of mouse and human myelinated inhibitory axons supports the mouse as a good model system to study disease-related changes of cortical myelin.

1. Micheva KD, Wolman D, Mensh BD, Pax E, Buchanan J, Smith SJ, Bock DD. (2016) A large fraction of neocortical myelin ensheathes axons of local inhibitory neurons. Elife. 2016 Jul 6;5. pii: e15784

Disclosures: K.D. Micheva: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aratome LLC. **E.F. Chang:** None. **A.L. Nana:** None. **W.W. Seeley:** None. **J.T. Ting:** None. **C. Cobbs:** None. **E. Lein:** None. **S.J. Smith:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aratome LLC. **R.J. Weinberg:** None. **D.V. Madison:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.22/M2

Topic: B.11. Glial Mechanisms

Support: NINDS NS104478

Title: Astrocyte depolarizations modulate astrocytic glutamate clearance in a Kir4.1 dependent manner

Authors: *M. ARMBRUSTER[1], C. G. DULLA[2]
[1]Neurosci., Tufts Univ., Boston, MA; [2]Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Astrocytes abundantly express the voltage dependent glutamate transporters GLT-1 and GLAST, which rapidly remove glutamate from the extracellular environment following synaptic activity, and restrict the temporal and spatial extent of glutamate signaling. We previously showed that neuronal activity slows glutamate clearance in a local, stimulus number dependent, and glutamate independent manner. We hypothesize that this modulation is due neuronally induced astrocytic depolarizations by changes in extracellular K+, which are then cleared by the inward rectifying potassium channel Kir4.1. Somatic electrophysiology recordings from astrocytes show only limited and slow depolarizations of astrocytes. However, imaging new genetically encoded, astrocytically targeted, fluorescent voltage sensors in the adult mouse cortex reveals faster stimulus induced membrane depolarizations. In order to perturb the stimulus induced astrocytic changes; we have turned to the astrocytic potassium channel Kir4.1. Neuronal activity is thought to increase extracellular K^+, which is then cleared/buffered by astrocytes through Kir4.1. Kir4.1 expression and mutations have been associated with hyperexcitability and epilepsy. Through viral overexpression and pharmacological blockade of Kir4.1 in the adult mouse cortex, we have investigated how Kir4.1 levels and function modulate astrocytic glutamate clearance, as a proxy for peripheral depolarizations. Using NMDA current readouts of glutamate clearance, we show that Kir4.1 levels and function can bidirectionaly modulate the stimulus number dependent slowing of glutamate clearance (increased Kir4.1 = reduced slowing of glutamate clearance). These experiments use novel techniques and highlight new glial-neuron interactions, new mechanisms of modulating synaptic signaling, and new insights into astrocyte biology.

Disclosures: M. Armbruster: None. **C.G. Dulla:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.23/M3

Topic: B.11. Glial Mechanisms

Support: RO1MH067121

Title: The role of astrocytic ephrin-B1 in activity dependent synapse remodeling during memory formation

Authors: *S. WOODRUFF, J. KOEPPEN, A. NGUYEN, I. ETHELL
UC Riverside, Riverside, CA

Abstract: Astrocytes are glial cells known to regulate the formation, pruning, and maintenance of synapses. However, signals that facilitate astrocyte-mediated synaptic pruning are still unknown. Previous work in our lab suggest ephrin-B1 signaling in astrocytes mediates pruning of synapses through interactions with neuronal EphB receptors. Synaptosome engulfment by primary astrocytes is significantly impaired after inhibition of ephrin-B1 signaling in astrocytes or deletion of neuronal EphB receptors *in vitro*. Previous studies *in vivo* show deletion of astrocytic ephrin-B1 increases the number of excitatory synapses in the CA1 hippocampus and increased contextual recall. Our lab has also shown that overexpression of astrocytic ephrin-B1 results in reduced contextual recall, suggesting astrocytic ephrin-B1 may inhibit memory formation by eliminating excitatory synapses. This study looks at the differences in excitatory synapses in the CA1 hippocampal neurons activated during contextual recall in proximity to normal astrocytes and astrocytes overexpressing ephrin-B1 using adeno-associated viral (AAV) approach. Given the role of astrocytes and ephrin signaling in neurodevelopmental disorders and neurodegenerative diseases, this project has potential for future therapeutic clinical applications.
This work was supported by the NIH grant RO1MH067121.

Disclosures: S. Woodruff: None. **J. Koeppen:** None. **A. Nguyen:** None. **I. Ethell:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.24/M4

Topic: B.11. Glial Mechanisms

Support: ANII-SNB (Uruguay)
SNI (Uruguay)
PEDECIBA (Uruguay)
UdelaR (Uruguay)

Title: Reorganization of perineuronal nets and astrocyte phenotype in the rat's Medial Preoptic Area

Authors: *J. NOGUEIRA BORDE[1], D. MÉNDEZ[1], M. M. FERREÑO, 11600[2], N. URIARTE[2]
[1]Facultad de Medicina Univ. De La República, Montevideo, Uruguay; [2]Facultad de Ciencias, Univ. de la República, Montevideo, Uruguay

Abstract: Perineuronal nets (PNNs) are aggregations of extracellular matrix associated to specific neuronal populations in the CNS, suggested to play key roles in neural development, synaptogenesis, neuroprotection and experience-dependent synaptic plasticity. PNN remodeling during natural plastic processes in adults and its potential regulatory role in neuro-glia interaction

are poorly understood. Pregnancy and lactation are characterized by a remarkable increase in neuroplasticity, however it is unknown how PNNs remodeling occurs at maternal circuits during these periods. We analyzed the PNN expression and astrocyte associated phenotype remodeling in a key nucleus of the maternal circuit, the medial preoptic area (mPOA). Brains of female rats were obtained during estrous cycle (di-por-estrous, n=7), pregnancy (Gestation Day (GD) 10, GD14, GD21, n=7) and postpartum period (Postpartum Day (PPD) 2, PPD14 and PPD 22, n=7). mPOA containing slices were processed with a) *Wisteria floribunda* lectin (WFA) for labeled chondroitin sulphate glycosaminoglycan (an structural PNN component), and b) Cy3 coupled anti-GFAP (Glial fibrillary acidic protein) forto analyze astrocyte phenotype. Neither PNNs nor diffuse extracellular matrix expression was detected on mPOA of virgin rats. At GD10 few neurons started to express PNN at the soma and dendrites simultaneously, with almost no interneuronal diffuse extracellular matrix. The number of PNN expressing neurons increases reaching a maximum at GD21. PNN dissipate post partum in an orderly manner, first dendrites (PPD2) then soma (PPD14), with a concurrent increase of interneuronal diffuse extracellular matrix expression (PPD14-18). Interestingly, preliminary results show an increase in GFAP expressing astrocytes associated to PNN assembly (GD 10, 14, 21 n=2) that persists at PPD2, gradual returning to basal level during lactation (PPD 14, 22, n=2). The different organization of PNNs is associated with changes in the plasticity of the mPOA, most likely underlying the dynamics of maternal behavior and physiological adaptations to lactation. Assembly and disassembly showed different dynamics, and were accompanied by astrocyte phenotype remodeling, suggesting the plasticity of neuro-astrocyte interactions.

Disclosures: J. Nogueira Borde: None. **D. Méndez:** None. **M.M. Ferreño:** None. **N. Uriarte:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.25/M5

Topic: B.11. Glial Mechanisms

Support: British Heart Foundation (Ref: PG/13/79/30429)
Wellcome Trust
Marie Curie Actions (Ref: 654691)

Title: Processing of afferent information at the level of NTS: Astrocytic ATP release evoked by afferent stimulation modulates baroreflex sensitivity

Authors: *S. MASTITSKAYA[1], P. S. HOSFORD[1], N. MARINA[1], S. KASPAROV[2], A. G. RAMAGE[1], A. V. GOURINE[1]

[1]Neuroscience, Physiol. and Pharmacol., Univ. Col. London, London, United Kingdom; [2]Univ. of Bristol, Bristol, United Kingdom

Abstract: Astrocytes play an important role in cardiovascular reflex integration at the level of the nucleus of the solitary tract (NTS, Lin et al., 2013, *J Neurosci*. 33:18608-17), but underlying mechanisms remain poorly understood. ATP, a prototypical gliotransmitter, excites GABAergic interneurons to increase synaptic inhibition in various CNS areas (Bowser and Khakh, 2004, *J Neurosci*. 24:8606-20; Torres et al., 2012, *J Sci Signal.* 5(208):ra8). In this study we investigated the role of NTS astrocytes and ATP, acting though P2Y1 receptors, in the modulation of baroreceptor reflex pathway. Astrocytic vesicular release mechanisms were disrupted in the NTS by expression of dnSNARE driven by adenoviral vector under the control of an enhanced GFAP promoter. Arterial blood pressure and heart rate were recorded using biotelemetry (DSI). Baroreceptor reflex gain (sBRG) was determined from spontaneous changes in blood pressure and pulse interval during normal behavior. In α-chloralose-anaesthetized rats, baroreflex sensitivity was determined following norepinephrine infusion (1 μg/kg, i.v.) to activate the depressor reflex. P2Y1 receptors in the NTS were blocked by topical application of a selective antagonist MRS-2500 (5 μM). In animals transduced to express dnSNARE in the NTS astrocytes (n=5), the sBRG significantly increased when assessed on day 7 after viral injections (1.7±0.1 bpm/mmHg) compared to baseline values (1.0±0.1 bpm/mmHg, $p<0.01$) and sBRG recorded in animals transduced to express eGFP in the NTS (controls, 1.2±0.1 bpm/mmHg, $p<0.05$). Activation of baroreflex in anaesthetized rats (n=4) was associated with increase in mean arterial pressure of 45±5 mmHg and a decrease in HR of 51±7 bpm (BRG 1.1±0.1 bpm/mmHg). Blockade of NTS P2Y1 receptors augmented the degree of bradycardia induced by baroreceptor activation with systemic norepinephrine (BRG 1.5±0.3 bpm/mmHg, $p<0.05$). These data demonstrate that blockade of vesicular release in the NTS astrocytes increases baroreflex sensitivity. We hypothesize that in response to incoming afferent information NTS astrocytes release ATP which restricts the expression of baroreflex via activation of P2Y1 receptors on local inhibitory interneurons.

Disclosures: P.S. Hosford: None. **N. Marina:** None. **S. Kasparov:** None. **A.G. Ramage:** None. **A.V. Gourine:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.26/M6

Topic: B.11. Glial Mechanisms

Support: NIMH K01MH087845
Brain Behavior Research Foundation NARSAD Young Investigator Award

UL Lafayette Undergraduate Research Grant
UL Lafayette Graduate Student Organization

Title: Disrupted astrocyte interneuron communication in astrocytes lacking fibroblast growth factor receptor 1

Authors: *K. M. SMITH[1], N. A. ESTEVE[1], N. M. DUNN[2], M. A. HENDRICK[2], D. J. ROGERS[3]
[2]Biol., [1]Univ. of Louisiana At Lafayette, Lafayette, LA; [3]Biol., Univ. of Louisiana at Lafayette, Lafayette, LA

Abstract: Fibroblast Growth Factor Receptor 1 (FGFR1) plays important roles in central nervous system development, and is highly expressed within cortical astrocytes. Neuron-astrocyte communication is vital to the proper functioning of the central nervous system. We have previously demonstrated that Cocultures of GABAergic interneurons grown on *FGFR1Flox/Flox;HGFAPCre+* knock out cortical astrocytes displayed smaller soma size, fewer number of neurites, and a more immature phenotype. Changes in neuronal growth may reflect the lack of FGFR1 or may be influenced by dysfunctional neuron-astrocyte communication from impaired astrocytes. FGFR1 kinase signaling initiates many intracellular signaling pathways involving cell differentiation, cell proliferation, and calcium signaling, interruption of this pathway may inhibit the effective function of the astrocyte in its communication with GABAergic interneurons. Comparing astrocyte cultures to GABAergic interneuron-astrocyte cocultures using cortical astrocytes from *FGFR1Flox/Flox;NestinCre+* and control p2-4 mice, calcium imaging of physiological responses were studied. Genotype had no effect on number of spontaneous calcium waves duration, while the intensity of calcium waves was significantly increased in astrocytes lacking Fgfr1 (p=0.0001). Treatment of cultures with 25μM Glutamate increased the frequency (p=0.004) and intensity (p=0.032) of calcium waves in controls and FGFR1 KO astrocytes. When GABAergic interneuron-astrocyte cocultures were treated with 25μM Glutamate, a decrease in calcium wave frequency (p=0.035) and duration (p=0.022) occurred in Fgfr1 KO astrocytes (p=0.035), while no difference was observed in control astrocytes. The decreased signaling in response to 25μM Glutamate in astrocytes may be due to GABA signaling from the interneurons. This will be confirmed through testing with GABA and the GABAergic antagonists; Bicuculline and CGP36216. We will further examine if the effects of Glutamate stimulation on the co-cultures is mediated by ionotropic *versus* metabotropic glutamate receptors.

Disclosures: N.A. Esteve: None. **N.M. Dunn:** None. **M.A. Hendrick:** None. **D.J. Rogers:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.27/M7

Topic: B.11. Glial Mechanisms

Support: BrightFocus Foundation
Alzheimer's Drug Discovery Foundation
The Harrington Discovery Institute
NIA (1 U01 AG054444-01A1

Title: Pyridazine-derivatives enhance structural and functional plasticity of tripartite synapse via activation of local translation in astrocytic processes

Authors: *J. B. FOSTER[1], F. ZHAO[1], X. WANG[1], C. C. ASKWITH[1], K. J. HODGETTS[2], C.-L. G. LIN[1]
[1]Neurosci., The Ohio State Univ., Columbus, OH; [2]Brigham and Women's Hosp. and Harvard Med. Sch., Cambridge, MA

Abstract: Excitatory amino acid transporter 2 (EAAT2) is primarily located in perisynaptic astrocytic processes (PAP) where it plays a critical role in synaptic glutamate homeostasis. Dysregulation of EAAT2 at the translational level has been implicated in a myriad of neurological diseases. We previously discovered that pyridazine analogs can activate EAAT2 translation. Here, we sought to further refine the site and mechanism of compound action. We found that *in vivo*, compound treatment increased EAAT2 expression only in the PAP of astrocytes where EAAT2 mRNA also was identified. Direct application of compound to isolated PAP induced *de novo* EAAT2 protein synthesis, indicating that compound activates translation locally in the PAP. Using a screening process, we identified a set of PAP proteins that are rapidly up-regulated following compound treatment and a subset of these PAP proteins may be locally synthesized in the PAP. Importantly, these identified proteins are associated with the structural and functional capacity of the PAP, indicating compound enhanced plasticity of the PAP. Concomitantly, we found that pyridazine analogs increase synaptic protein expression in the synapse and enhance hippocampal long-term potentiation. This was not dependent upon compound-mediated local translation in neurons. This suggests that compound enhances the structural and functional capacity of the PAP which in turn facilitates enhanced plasticity of the tripartite synapse. Overall, this provides insight into the mechanism action site of pyridazine-derivatives as well as the growing appreciation of the dynamic regulation and functional aspects of the PAP at the tripartite synapse.

Disclosures: J.B. Foster: None. **F. Zhao:** None. **X. Wang:** None. **C.C. Askwith:** None. **K.J. Hodgetts:** None. **C.G. Lin:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.28/M8

Topic: B.11. Glial Mechanisms

Support: National Institutes of Health
UC Riverside

Title: The role of hippocampal astrocytic swelling on neuronal hyperexcitability in conditions of elevated potassium

Authors: *E. M. WALCH[1], N. CUVELIER[2], T. R. MURPHY[5], D. DAVILA[2], A. VENKATESH[6], I. M. HOLMAN[3], C. KHACHATUROVA[2], T. A. FIACCO[4]
[1]Univ. of California Riverside, Moreno Valley, CA; [3]Neurosci., [4]Cell Biol. & Neurosci., [2]UC Riverside, Riverside, CA; [5]Div. of Biomed. Sciences, Sch. of Med., [6]Neurosci., Univ. of California, Riverside, Riverside, CA

Abstract: Pathological hyperexcitability of neurons has been linked to both cellular swelling and increased extracellular potassium ($[K^+]_o$). However, the identity of the swelling cells and the effects of cell-type specific swelling on neuronal excitability in elevated $[K^+]_o$conditions are poorly understood. Astrocytes regulate $[K^+]_o$ by selective uptake through astrocyte-specific K^+ channels, and are thus likely candidates for high $[K^+]_o$ induced cell swelling and subsequent reduction of the extracellular space (ECS). Our work suggests that $[K^+]_o$ in the range of 6.5 - 26 mM produces selective swelling of astrocytes, and this swelling increases proportionally with increasing $[K^+]_o$ concentrations. Neuronal volume is almost completely unaffected by elevated $[K^+]_o$ and actually shrink slightly in hyperosmolar 26 mM $[K^+]_o$ (elevated $[K^+]_o$ not balanced by equiosmolar reduction of $NaCl_2$).. Pharmacological experiments using barium chloride suggest that astrocyte swelling is independent of inwardly rectifying potassium channels, which are thought to be key for astrocytic regulation of extracellular $[K^+]_o$. These channels are thought to function in tandem with the astrocyte-specific aquaporin 4 (AQP4) channel, but genetic knockout of AQP4 also revealed that high $[K^+]_o$ induced astrocyte swelling is independent of AQP4. Further experiments are underway in attempt to define the mechanism of astrocyte-specific swelling in high $[K^+]_o$, including targeting leak 2-pore K^+ channels, the Na^+/K^+ ATPase, the sodium-bicarbonate cotransporter (NBC), and the NKCC/KCC cotransporters. Additional experiments are ongoing to explore the effects of high $[K^+]_o$ induced astrocytic swelling on excitability of CA1 pyramidal neurons in TTX conditions to prevent direct depolarization-induced increases in neuronal firing. Last, we have also begun to develop optogenetic approaches to swell astrocytes selectively by generating an osmotic gradient to draw water into astrocytes coupled to nonselective cation influx. These experiments are expected to shed light

onto the mechanisms underlying selective astrocyte swelling in high $[K^+]_o$ and the impact of high $[K^+]_o$ -induced astrocyte swelling on neuronal excitability.

Disclosures: E.M. Walch: None. **N. Cuvelier:** None. **T.R. Murphy:** None. **D. Davila:** None. **A. Venkatesh:** None. **I.M. Holman:** None. **C. Khachaturova:** None. **T.A. Fiacco:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.29/M9

Topic: B.11. Glial Mechanisms

Support: NSF HBCU-UP RIA (HRD 1401026)
NIH-COBRE (1P20GM103653-01A1)
NIH-NINDS R25 (R25NS09537)

Title: Molecular mechanisms of astrocyte-neuron interactions in the development of synchronized activity in neuronal networks

Authors: G. GUEVARA, K. R. SANCHEZ, J. SUN, M. A. HARRINGTON, *M. TEMBURNI
Biol., Delaware State Univ., Dover, DE

Abstract: Synchronous oscillations are necessary for establishing functional neuronal networks in normal vertebrate brain development - however, the mechanisms of neuronal synchronization are not fully understood. Existing models of synchronous activity assume that it is intrinsic to neurons. Astrocytes have been shown to modulate oscillatory activity in networks of neurons possibly by releasing like glutamate and ATP. We have established pure and mixed (astrocyte and neuronal) cultures from the developing chicken brain (optic tectum) and recorded neuronal network activity using two different the multi-electrode array systems, MED64 and Axion. Our preliminary results indicate that astrocytes are necessary for synchronous activity of neurons in culture. Mixed neuron and astrocyte cultures on multi-electrode arrays (MEAs) show random spiking activity which synchronizes over time whereas astrocyte-free neurons only show random activity without synchronization. Our results validated that the physical presence of astrocytes is required to properly establish synchronized activity in neuronal networks. To further dissect the molecular pathways involved, we targeted the metabotropic glutamate receptor (mGluR) pathway within astrocytes as crucial for communication with neurons. Our model predicts that glutamate sensing at tripartite synapses via mGluRs elevates local calcium within astrocyte processes. With sufficient activation, the localized calcium elevation crosses a threshold causing a global calcium release within the astrocyte leading to the exocytosis of glutamate. We proposed to test this model by disrupting the mGluR pathway within astrocytes using a truncated mGluR subunit (mGluR DN) which acts as a dominant negative blocking downstream signaling.

Astrocytes expressing the mGluR DN are expected to have reduced or no calcium elevation upon mGluR stimulation. We have generated astrocyte lines expressing the mGluR dominant negative (mGluR DN) along with the calcium sensor GCaMP5G and the glutamate sensor iGluSnFR. With these tools a more comprehensive molecular model for astrocyte involvement in the generation of neuronal synchrony can be developed.

Disclosures: G. Guevara: None. **K.R. Sanchez:** None. **J. Sun:** None. **M.A. Harrington:** None. **M. Temburni:** None.

Poster

652. Glial Mechanisms: Glia-Neuron Interactions: CNS

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 652.30/M10

Topic: B.11. Glial Mechanisms

Support: NIDA Grant 5R00DA040004-04

Title: Effects of heroin on neuron-astrocyte interaction

Authors: *M. D. SCOFIELD
Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Addiction is commonly associated with modification of communication between the prefrontal cortex (PFC) and the nucleus accumbens. This drug-induced alteration, among others, is thought to contribute to the persistent relapse vulnerability that characterizes addiction. One unique aspect of how drug exposure alters synaptic plasticity in the nucleus accumbens is that several of the molecular adaptations that contribute to the altered synaptic communication described above, occur specifically in astroglia. As the study of astrocyte biology in the context of drug addiction progresses, these astrocytic cellular processes impacted by drug abuse and drug cues may serve as candidates for biological mediators of relapse vulnerability and also as potential targets for therapeutic intervention. Indeed, drugs like N-acetylcysteine (NAC) which act to reverse drug-induced molecular alterations in NAcore astroglial glutamate systems, serve as potent inhibitors of cued relapse in animal models. In parallel to the recent advancements in our understanding of the connection between dendritic spine morphology and the synaptic plasticity underlying relapse in the NAcore, we are beginning to see the study of the morphological properties of astrocytes in the context of drug addiction provide similar insights. Using AAV5-GFAP-LCK-GFP labeled astrocytes, Synapsin I immunolabeling and confocal microscopy, we have recently shown that accumbens astrocytes withdrawal from NAcore synapses following extinction of heroin seeking, an effect that likely exacerbates drug-induced deficits in astroglial glutamate clearance linked to relapse vulnerability. Here we explore the association of astrocytes with synapses in the prelimbic cortex following heroin exposure and

after NAC treatment using the same strategy. As an extension of these analyses, we have also examined astrocyte-dendritic spine proximity in cortical neurons that project to the NAcore, using AAV-based retrograde viral labeling of neurons and AAV5-GFAP-LCK-GFP labeling of astrocytes following extinction of heroin self-administration. Taken together our data suggest that the alterations in the association of astrocytic processes with synapses caused by exposure to drugs of abuse may serve an emerging crucial mediator of relapse biology.

Disclosures: M.D. Scofield: None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.01/M11

Topic: B.12. Demyelinating Disorders

Support: 973 GRANT, 2010CB835400, Chinese Ministry of Science and Technology

Title: Mixed lineage kinase domain-like protein MLKL breaks down myelin following nerve injury

Authors: *C. PAN, Z. YING, S. CHEN, Z. JIANG, F. WANG, X. WANG
Natl. Inst. of Biol. Sciences, Beijing, Beijing City, China

Abstract: Myelin breakdown happens in demyelinating diseases as well as in nerve injury. In demyelinating diseases, aberrant myelin loss is caused by genetic deficiency, infection or autoimmune responses, resulting in reduced transduction efficiency of action potential and axon degeneration. In response to nerve injury, myelin needs to be cleared in time to facilitate axon regeneration. The exact mechanism of the execution of myelin breakdown is unclear in both cases. Unleashing the mechanism of myelin breakdown is crucial for understanding the pathologic mechanism of demyelinating diseases and the regulation of nerve regeneration.
In the current work, we used a model of peripheral sciatic nerve injury to study the mechanism of myelin breakdown. We found that the mixed lineage kinase domain-like protein (MLKL), a protein previously reported to execute necroptosis, executed myelin breakdown following sciatic nerve injury. MLKL expression is induced in Schwann cells after the injury. The rate of myelin breakdown of sciatic nerve in *Mlkl* knockout mice is significantly slower than in wild-type mice. In the presence of nerve injury signal, MLKL is activated through a phosphorylation event on a serine residue in its pseudokinase domain, then inserts into myelin sheath membrane via binding with sulfatide, and finally breaks down the myelin. This MLKL mediated myelin breakdown is necessary for axon regeneration. *Mlkl* knockout mice have a poorer regeneration capability compared with wild-type mice. Overexpression of MLKL in sciatic nerve of wild-type mice can accelerate its functional recovery after injury.

Disclosures: C. Pan: None. **Z. Ying:** None. **S. Chen:** None. **Z. Jiang:** None. **F. Wang:** None. **X. Wang:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.02/M12

Topic: B.12. Demyelinating Disorders

Support: Intramural research program of the Eunice Kennedy Shriver NICHD, NIH.

Title: Schwann cell-specific deletion of phosphatidylinositol 4-kinase type IIIα (PI4KA) alters actin dynamics contributing to severe myelination defects in mice

Authors: *A. ALVAREZ-PRATS, Y. KIM, T. BABA, D. ABEBE, T. BALLA
Section on Mol. Signal Transduction. Program for Developmental Neurosci., Eunice Kennedy Shriver NICHD, NIH., Bethesda, MD

Abstract: Myelination is a complex physiological process carried out by specialized Schwann cells (SCs) in the peripheral nervous system (PNS), and several human neuropathies, such as Charcot-Marie-Tooth Disease, show myelination impairment within the PNS. Myelin is composed of a defined mixture of proteins and phospholipids but how SCs regulate and execute their lipid synthetic and distribution programs during myelination are poorly understood. Recent studies have highlighted the critical role of phosphatidylinositol 4-phosphate (PI4*P*) gradients in controlling the non-vesicular transport of several key phospholipids between cellular membranes. Moreover, PI4P, made in the plasma membrane (PM) by phosphatidylinositol 4-kinase type IIIα (PI4KA), also serves as the precursor of the important signaling phospholipids PI(4,5)P_2 and PI(3,4,5)P_3. Both of these lipids are known to regulate cellular movements via controlling actin dynamics, and up-to-date studies have shown that actin plays a crucial role during myelination. We have recently showed that SC-specific deletion of PI4KA in mice affects myelination within the PNS through a mechanism that affects PI4*P* synthesis and transport but appears to spare PI(4,5)P_2 generation and PI(3,4,5)P_3 signaling. Here, we show that deletion of PI4KA in SCs has a major impact on the development of important actin-based structural features of peripheral nerves, including malformation of Schmidt-Lanterman incisures (SLIs) and nodes of Ranvier. Experiments performed in a mouse SC line showed that prolonged inhibition (16 h) of PI4KA with a selective small molecule inhibitor caused a major disruption of actin stress fibers with significant accumulation of the cortical actin cytoskeleton. Remarkably, this phenomenon started to take place as soon as 15 min after the addition of the inhibitor. Genetic inactivation of the kinase, using MEF cells isolated from embryos of our pi4ka-flox mice, also showed major disruption of actin stress fibers and significant accumulation of the cortical actin cytoskeleton. PI4KA inhibition also affected the migration of cultured SCs toward

serum containing media without alteration of the PI3K pathway. Altogether, these data suggest a close direct connection between the activity of PI4KA, actin homeostasis, and myelination of the PNS. To our knowledge, this is the first study to reveal a direct role for PI4KA and PI4*P* in the control of cellular actin dynamics. Ongoing studies are aimed at understanding the molecular basis of the actin regulatory defect and delineating the mechanism by which changes in cortical actin on the expense of stress fibers alter the progression of myelination within the PNS.

Disclosures: A. Alvarez-Prats: None. **Y. Kim:** None. **T. Baba:** None. **D. Abebe:** None. **T. Balla:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.03/M13

Topic: B.12. Demyelinating Disorders

Title: The mechanism of central nervous system (CNS) remyelination promoted by circulating TGF-beta

Authors: *H. MACHIKA[1], R. MURAMATSU[1,2], T. YAMASHITA[1]
[1]Mol. Neurosci., Osaka Univ., Suita, Japan; [2]Mol. Pharmacol., Natl. Inst. of Neuroscience, Natl. Inst. of Neurol. and Psychiatry, Kodaira, Japan

Abstract: Remyelination, the reconstitution of myelin sheaths in the CNS, is a process to restore salutatory conduction and promote functional recovery after demyelination. Although remyelination requires oligodendrocyte differentiation, how oligodendrocyte differentiation is promoted is not fully clarified. It is known that blood brain barrier disrupted around the demyelinated lesion sites and circulating blood components leaked out from the vasculature into the CNS. Therefore, in this study, we focused on the circulating blood components as the candidate molecules promoting oligodendrocyte differentiation.
We cultured oligodendrocyte precursor cells (OPCs) obtained from postnatal mice brain in the medium containing adult mice serum and quantified myelin basic protein (MBP) expression which is the constituent protein of myelin. We found that serum increase the MBP expression and assumed that some factors promoting oligodendrocyte differentiation is involved in the adult mice serum. By pharmacological screening, we found that TGF-beta1 in the serum drives MBP expression. Then, we identified that TGF-beta receptor was expressed in mature oligodendrocyte, but not in precursor cells and that TGF-beta receptor deficit from oligodendrocyte suppressed remyelination. We also found that specific depletion of circulating TGF-beta suppressed remyelination. These data suggest that TGF-beta from systemic environment effects on mature oligodendrocytes and promotes remyelination. Furthermore, we observed TGF-beta receptor expression in human oligodendrocytes using the autopsied brain of

multiple sclerosis patients. To confirm whether human oligodendrocytes have TGF-beta sensitivity, we supplied TGF-beta to human oligodendrocytes and then the expression of some myelin related genes were facilitated. Hence, TGF-beta might be common signal in oligodendrocytes differentiation between rodents and human.

Disclosures: H. Machika: None. **R. Muramatsu:** None. **T. Yamashita:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.04/DP04/M14

Topic: B.12. Demyelinating Disorders

Support: EPSRC Award ref 1668723
The Multiple Sclerosis Society

Title: Neuroinflammation causes changes to the nodes of Ranvier in multiple sclerosis normal appearing white matter

Authors: *P. GALLEGO DELGADO[1], R. REYNOLDS[1], A. A. FAISAL[2], J. MENG[3], R. JAMES[3], E. BROWNE[3]
[1]Imperial Col. London, London, United Kingdom; [2]Imperial Col. London, London, United Kingdom; [3]Imperial Col., London, United Kingdom

Abstract: In addition to the focal demyelinating lesions that are characteristic of multiple sclerosis (MS), both imaging and neuropathological analyses have demonstrated the presence of a more diffuse pathology in both the white and grey matter, including changes to the structure of nodes of Ranvier in the normal appearing white matter (NAWM). The presence of the tight axo-glial glial junctions of the myelin end loops and the proper clustering of sodium channels (Nav) at the node and potassium channels (Kv1.2) at the juxtaparanode are crucial for fast action potential conduction. In order to study the functional consequences of these nodal changes and to investigate the role of inflammation, we have examined the spatial expression of Caspr1, NF155, Nav, Kv1.2 and SMI32 in NAWM areas from post-mortem progressive MS brains (n=20 cases comprising 34 blocks with 340 NAWM areas) compared to non-neurological controls (n=10 cases comprising 16 blocks with 160 WM areas). To determine axo-glial abnormalities, intensity profiles were measured for each nodal parameter. This axo-geometrical data was then integrated into a computational model of an axon, which was developed with NEURON incorporating published electron-microscopy data from human and macaque brains. To test our hypothesis, rats were injected into the cerebral subarachnoid space with lentiviral vectors for lymphotoxin-α and interferon-γ and nodal changes examined 3 months later. The paranodes in the MS NAWM tissue were 21.7% longer on average than in the control, and associated with stressed axons and

activation of microglia. Moreover, the MS paranodes longer than 5µm were 76.28% more frequent than in the control tissue. In addition, we found a higher proportion of axons in MS NAWM with Kv 1.2 channels dislocated towards the paranode, which correlated with paranodal elongation. When these changes were inserted into the computational model, assuming that the observed increment of paranodal length corresponded to an increment in the peri-axonal space of the paranodal and juxtaparanodal compartments, we observed an exponential decrease in conduction velocity as the paranodal peri-axonal space increases. Furthermore, we predicted a potential conduction failure when the peri-axonal space at the juxtparanode and paranode is increased up to a certain threshold in axons less than 1µm of diameter. The same changes in paranodal length and Kv channel dislocation were observed in the corpus callosum of rats with meningeal inflammation and chronic microglial activation, which points to microglia/astrocyte secretion of cytokines, glutamate and ROS as possible factors that could trigger these changes.

Disclosures: P. Gallego Delgado: None. **R. Reynolds:** None. **A.A. Faisal:** None. **J. Meng:** None. **R. James:** None. **E. Browne:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.05/M15

Topic: B.12. Demyelinating Disorders

Support: 18-BR-01-02

Title: An astrocytic membrane protein, MLC1 inhibits cell motility for stable cell communication

Authors: *J. HWANG, H.-H. LIM
KBRI, Daegu, Korea, Republic of

Abstract: Megalencephalic leukoencephalopathy with subcortical cysts (MLC) disease is a rare type progressive leukodystrophy in children. Mutation of MLC1 mainly lies behind of this disorder leading vacuolation of myelin and astrocyte, subcortical cysts, brain edema, and macrocephaly. Recent studies indicate that functional interactions between MLC1, GlialCAM, and ClC-2 channel is important to regulate neuronal, glial, and vascular homeostatic interactions, however, the physiological role of MLC1 on the cellular communication is poorly understood. Thus, we have been trying to reveal the molecular function of MLC1 on the cell to cell interaction. Expression of MLC1 drastically altered cell morphology; disappearance of lamellipodia and increase in filopodia. Moreover, wound healing assay and live cell time-lapse imaging revealed that cell motility was significantly suppressed by MLC1. These changes in cell morphology and motility seemed to be correlated with altered cellular actin dynamics.

Interestingly, patient-derived MLC1 mutants did not affect cell morphology and motility and the expression pattern of mutants were mainly accumulated in the intracellular organelles. These data suggested that expression of MLC1 on the plasma membrane might change actin dynamics, cell shape and cell motility. Indeed, we found that MLC1 shows heteromorphic intracellular distribution patterns during the course of expression. Plasma membrane-localized MLC1 (PM-MLC1) induced stationary movement, however, intracellular organelle-localized MLC1 (IO-MLC1) showed normal cell motility. These results indicate that MLC1 is important to regulate cell motility and stabilizing cell-cell interaction. In MLC disease patients, misallocation of mutant MLC1 could related with unstable cell communication resulting in disturbed homeostasis of neuro-glia-vascular interaction.
Keywords: Neurovascular unit; MLC1; Cell motility; Actin branching; Cell communication

Disclosures: J. Hwang: None. **H. Lim:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.06/M16

Topic: B.12. Demyelinating Disorders

Support: NIH Grant 1R21NS083042

Title: NAA depletion rescues myelin degeneration in the Canavan disease mouse model Aspa^{nur7} but results to hypomyelination and lethality

Authors: *M. TRAKA[1], M. BARNEY[2], B. PARDO[3]
[1]Anat., Midwestern Univ., Downers Grove, IL; [2]Neurol., Univ. of Chicago, Chicago, IL; [3]Mol. Biology, Ctr. for Mol. Biol. Severo Ochoa UAM-CSIC, Autonomous Univ. of Madrid, Madrid, Spain

Abstract: Canavan disease (CD) is a rare autosomal recessive leukodystrophy that is caused by mutations of the aspartoacylase gene (*ASPA*). ASPA is highly expressed in mature oligodendrocytes, where it catalyzes the hydrolysis of the most abundant amino acid in the brain, N-acetyl-aspartate (NAA) to acetate and aspartic acid. ASPA deficiency in CD results in high levels of NAA in the CSF and the urine of the CD patients. The disease pathology is characterized by severe spongiform degeneration of the myelin throughout the CNS that is manifested early postnatally. We previously described the identification of the ENU-induced nonsense mutation, Q193X, in the mouse *Aspa* gene that results in the absence of detectable ASPA protein expression in *Aspa^{nur7}* homozygous mutant mice, which display severe spongy degeneration (vacuolation) throughout the CNS, strikingly resembling CD. Similarly to CD, NAA is increased in the CNS of *Aspa^{nur7}* mutants. New evidence from our lab and others using

the *Aspa*^{nur7} mutants has shown that the mechanism of CD pathogenesis implicates the high NAA levels as a main cause of the myelin degeneration in CD. According to this hypothesis, the CD pathogenesis is caused by ASPA deficiency in mediating NAA clearance in the CNS and thereby protecting myelin and/or oligodendrocytes from NAA damage. This contradicts the other main hypothesis for CD that suggests a role of ASPA in supplying the NAA-derived acetate for myelin lipid synthesis. We generated ASPA-deficient mice that cannot synthesize aspartate and NAA due to a null mutation in the *Aralar/AGC1* transporter gene, the *Aspa*$^{nur7/nur7}$;*Aralar*$^{-/-}$ mice. Although NAA reduction rescues myelin degeneration in the CNS of the double mutants, these mice suffered from a severe, lethal neurological phenotype that is associated with CNS hypomyelination. Our data suggest that although NAA exerts a toxic effect on myelin and/or oligodendrocytes when present at high levels in Canavan disease, it may also play a critical role in supporting CNS myelination during development. To further understand the mechanism of CD pathogenesis, we are currently exploring the molecular pathways that are affected in the CNS of the *Aspa*^{nur7} homozygous mutant mice.

Disclosures: M. Traka: None. **M. Barney:** None. **B. Pardo:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.07/M17

Topic: B.12. Demyelinating Disorders

Title: Semaphorin4a causes oligodendrocyte cell death and demyelination

Authors: *B. CHIOU[1], E. LUCASSEN[2], A. KALLIANPUR[3,4], J. R. CONNOR[1]
[1]Neurosurg., [2]Neurol., Penn State Col. of Med., Hershey, PA; [3]Genomic Med., Cleveland Clinic/Lerner Res. Inst., Cleveland, OH; [4]Mol. Med., Cleveland Clin. Lerner Col. of Med., Cleveland, OH

Abstract: Dysregulated myelin production, demyelination, or hypomyelination by oligodendrocytes can lead to a variety of neurological defects, including both motor and cognitive deficits stemming from compromised action potential transmission. One of the primary reasons for irregular myelin deposition may revolve around the direct death of oligodendrocytes, however the causes for this death have yet to be discovered. Deficiency of trophic factors relating to the survival of oligodendrocytes, combined with direct interactions with the immune system, are favored paradigms that are increasingly implicated in demyelinating diseases of the central nervous system. Emerging members of immune-related molecules that have immune-mediated disease properties are proteins of the semaphorin family, such as Semaphorin4A (Sema4A). Implicated in diseases such as rheumatoid arthritis and asthma, the semaphorin family has been shown to be a key component of immune disease progression. We have

previously demonstrated that Sema4A is cytotoxic to rodent and human oligodendrocytes *in vitro*, signaling through the T-cell immunoglobulin and mucin domain (Tim-2) receptor in rodents and Tim-1 in humans. We also demonstrated that H-ferritin, the ubiquitous iron storage and delivery protein, also signals through Tim-1 and can be used to block Sema4A-mediated cytotoxicity. In our current work we demonstrate that intracranial infusion of Sema4A into the corpus callosum of wild-type mice causes robust demyelination coupled with decreased mature oligodendrocytes and increased microglia. These findings suggest Sema4A causes a direct cytotoxic effect *in vivo* on mature oligodendrocytes and that local microglia are responsive to this demyelination as well. Building upon our previous study, we assay for Sema4A in a significantly larger CSF cohort, again demonstrating significantly elevated Sema4A levels in the CSF of patients with altered white matter profiles. Taken together, our current work paired with our published work demonstrates Sema4A to be a significant mediator in the pathogenesis of demyelination and identifies a novel therapeutic targets in the treatment of demyelinating disorders.

Disclosures: B. Chiou: None. **E. Lucassen:** None. **A. Kallianpur:** None. **J.R. Connor:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.08/M18

Topic: B.12. Demyelinating Disorders

Support: NIH NINDS NS084303-01A1
NIH NINDS 1R01NS094522-01
FISM 2012/R/2
FISM 2015/R/7
The Miami Project To Cure Paralysis and the Buoniconti Fund

Title: Oligodendroglial TNFR2 regulates neuroinflammation and remyelination following CNS disease

Authors: *H. DESU[1], P. MADSEN[3], P. ILLIANO[4], M. PLASTINI[5], J. SHI[5], R. BRAMBILLA[2]
[2]The Miami Project to Cure Paralysis, Dept. of Neurosurg., [1]Univ. of Miami Miller Sch. of Med., Miami, FL; [3]Univ. of Rochester Med. Ctr., Rochester, NY; [4]Miami Project to Cure Paralysis, [5]Univ. of Miami, Miami, FL

Abstract: Tumor Necrosis Factor (TNF) is a pleiotropic cytokine involved in physiological and pathological processes. Among those, TNF has been implicated in the pathophysiology of various neurological disorders, including multiple sclerosis (MS). TNF exists in two forms, transmembrane (tmTNF) and soluble (solTNF), whose cellular effects are dependent upon which

receptor TNF binds to. Due to differing binding affinities, solTNF preferentially binds to TNF receptor 1 (TNFR1) and mediates detrimental processes such as apoptosis and chronic inflammation, while tmTNF preferentially binds to TNF receptor 2 (TNFR2) and mediates protective processes such as cell survival, regulation of inflammation, and remyelination. Our lab has significantly contributed to elucidating the complex role of TNF in CNS autoimmunity. By ablating TNFR2 from all oligodendrocyte lineage cells (CNP-cre:$TNFR2^{fl/fl}$ mice), we showed that TNFR2 promotes remyelination following EAE. Furthermore, CNP-cre:$TNFR2^{fl/fl}$ mice showed exacerbation of the acute phase of EAE, which is mainly driven by immune cell infiltration, suggesting that TNFR2 might play a role in regulating the immune-mediated neuroinflammatory response as well (Madsen et al., 2016). To elucidate the mechanisms through which oligodendroglial TNFR2 regulates remyelination and, possibly, neuroinflammation, we generated PDGFRα-cre^{ER}:$TNFR2^{fl/fl}$:EYFP mice to conditionally ablate TNFR2 in oligodendrocyte precursor cells (OPCs) and induce concomitant expression of EYFP. In the cuprizone model of demyelination, TNFR2 ablation in OPCs resulted in reduced numbers of newly formed myelinating oligodendrocytes once mice were restored to normal diet. This suggests that TNFR2 is important for OPC differentiation into mature oligodendrocytes. Furthermore, in the MOG_{35-55} EAE model of MS ablation of TNFR2 in OPCs resulted in earlier EAE onset and earlier peak disease, suggesting that oligodendroglial TNFR2 may be mediating the process by which peripheral immune cells infiltrate the CNS. Overall, our data point at oligodendroglial TNFR2 signaling as an important pathway in the modulation of neuroinflammation and remyelination in CNS disease, supporting the idea that TNFR2 could be a promising new target for MS therapy.

Disclosures: H. Desu: None. **P. Madsen:** None. **P. Illiano:** None. **M. Plastini:** None. **J. Shi:** None. **R. Brambilla:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.09/N1

Topic: B.12. Demyelinating Disorders

Support: NIH NINDS NS084303-01A1
NIH NINDS 1R01NS094522-01
NIH NEI 5R01EY010804
NIH NIA 1R01AG036871
NIH NINDS 1R01NS079965
The Miami Project To Cure Paralysis and the Buoniconti Fund

Title: Role of mitochondrial dysfunction in oligodendrocytes in the etiopathogenesis of multiple sclerosis

Authors: *M. PLASTINI[1], P. MADSEN[3], H. DESU[4], P. ILLIANO[2], C. MORAES[1], R. BRAMBILLA[5]
[2]Miami Project to Cure Paralysis, [1]Univ. of Miami, Miami, FL; [3]Univ. of Rochester Med. Ctr., Rochester, NY; [5]The Miami Project To Cure Paralysis, Dept. of Neurosurg., [4]Univ. of Miami Miller Sch. of Med., Miami, FL

Abstract: While neuronal mitochondrial dysfunction has been clearly implicated in the pathophysiology of multiple sclerosis (MS), the role of mitochondrial dysfunction in oligodendrocytes in MS has not been explored. To investigate this question we generated a mouse model where mitochondrial DNA (mtDNA) double-strand breaks (DSB) can be specifically induced in myelinating oligodendrocytes via the expression of the mitochondrial-targeted endonuclease mtPstI (PLP:mtPstI mice). Using this model, we previously showed that induction of mtDNA DSB causes impairments consistent with an MS-like phenotype, including demyelination and axonal damage (Madsen et al., 2017). Importantly, we demonstrated that mtDNA damage caused oligodendrocytes to undergo cell death. Our current studies are aimed at understanding the mechanisms by which oligodendrocytes die as a consequence of mtDNA damage. Specifically, we are evaluating whether this is directly dependent on impairment of the OXPHOS system or if other mechanisms, such as oxidative damage, are indirectly involved.To assess whether oxidative damage by reactive oxygen species, accumulated due to impaired OXPHOS, is responsible for oligodendrocyte death, we treated mice with the antioxidant N-Acetyl Cysteine (NAC), administered in the drinking water. Preliminary data show that, after 3 months of NAC exposure, treated PLP:mtPstI mice show a trend toward mild locomotor improvement compared to untreated mice. This suggests that oxidative stress might be contributing, at least in part, to oligodendrocyte death.Furthermore, to better characterize the pathological hallmarks of our PLP:mtPstI model, we performed flow cytometric studies to quantify the presence of immune cells in the CNS of induced PLP:mtPstI mice at 2 and 6 months of age. We observed an increased presence of B cells, neutrophils and macrophages in the spinal cord and cerebellum of PLP:mtPstI mice at 2 months. At 6 months B cells were still elevated in the CNS of PLP:mtPstI mice. This indicates that primary oligodendrocyte death elicits a secondary immune response, which can in turn participate in further damaging the CNS, in line with the “intrinsic hypothesis” of MS. As a result, our PLP:mtPstI mouse model not only can help shed light on the consequences of mitochondrial dysfunction in oligodendrocytes, but also proves a useful tool to model chronic demyelinating disease, hence serving as a platform for testing remyelinating therapies.

Disclosures: M. Plastini: None. **P. Madsen:** None. **H. Desu:** None. **P. Illiano:** None. **C. Moraes:** None. **R. Brambilla:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.10/N2

Topic: B.12. Demyelinating Disorders

Support: MedImmune PhD studentship

Title: A molecular characterisation of meningeal inflammatory infiltrates in progressive multiple sclerosis

Authors: *R. REYNOLDS[1], L. FUENTES-FONT[1], C. GLOVER[2]
[1]Imperial Col. London, London, United Kingdom; [2]MedImmune PLC, Cambridge, United Kingdom

Abstract: The presence of lymphoid-like immune cell aggregates in the leptomeninges is suggested to promote damage to the cerebral cortex and play a role in accumulating disability in multiple sclerosis. To explore the molecular mechanisms that drive their formation, cryosections were cut from five cortical blocks per case from 55 SPMS and 14 control brains. Meningeal tissue was dissected and RNA extracted. Affymetrix HTA 2.0 GeneChips were used to obtain the meningeal transcriptome and gene expression determined using R package Limma. Differentially expressed genes with FC>2 and FDR>0.05 were used to perform gene set enrichment analysis using WebGestalt and gene networks constructed using R package WGCNA. When comparing controls with highly inflamed MS cases, alterations were mainly found in expression of homing chemokines and receptors and in cytokines that enhance B cell survival, proliferation and antibody and IFNγ production, such as IL10, IL18, PPBP, CXCR4, HSPA7, XBP1, CS1 and CD27. Modifications in genes involved in the development of lymphatic vessels (LYVE1) and cell motility, survival and antigen presentation (HLA-B) were prominent. Functional pathway analysis identified significant involvement of pathways associated with *Th17, Th1/Th2 cell differentiation, haematopoietic and lymphoid organ development, cell adhesion and leukocyte migration.* Gene network analysis revealed 5 network modules whose eigengenes were highly correlated with disease status and lymphocytic infiltration. Functional enrichment yielded a list of functions, including cell adhesion, protein folding and pro-inflammatory processes. Subsequent to microarray data analysis a panel of 55 inflammatory genes was chosen for validation by TaqMan OpenArrays. Highly significant, strong and moderately strong, correlations were found between the TaqMan and Affymetrix data for most individual genes, providing robustness to our meningeal transcriptomics data. We have identified molecular cues that are likely to mediate meningeal inflammation in MS that suggest a dysregulation of pathways that are critical for B-cell trafficking and recruitment into the CNS.

Disclosures: **R. Reynolds:** 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.; MedImmune PLC. **L. Fuentes-Font:** None. **C. Glover:** A. Employment/Salary (full or part-time):; MedImmune PLC.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.11/N3

Topic: B.12. Demyelinating Disorders

Support: NIH Grant NS100459
NIH Grant NS034467
NIH Grant AG023084
NIH Grant AG039452
Foundation Leducq 16 CVD 05

Title: Pericyte deficiency leads to fibrin(ogen)-dependent white matter demyelination and axonal degeneration

Authors: *A. M. NIKOLAKOPOULOU[1], A. MONTAGNE[2], Z. ZHAO[3], A. P. SAGARE[4], D. LAZIC[2], Y. WANG[5], B. V. ZLOKOVIC[6]
[1]Physiol. and Biophysics, [3]Physiol. & Biophysics, [4]Dept. of Physiol. and Biophysics, [2]USC, Los Angeles, CA; [5]Zilkha Neurogenetic Inst., Keck Sch. of Med. At USC, Los Angeles, CA; [6]Zilkha Neurogenetic Inst., Keck Sch. of Med. of the Univ. of Southern California, Los Angeles, CA

Abstract: White matter damage is a characteristic of a plethora of neurodegenerative diseases, such as Alzheimer's disease (AD) and Multiple Sclerosis (MS). Pericytes play an important role in sustaining blood brain barrier (BBB) permeability and cerebral blood flow (CBF), while they participate in the clearance of toxic byproducts. Pericyte loss has been implicated in BBB breakdown, neuronal degeneration, cognitive impairment, inflammation, synaptic loss and has negative effects on CBF. In this study, we used *Pdgfrβ*$^{F7/F7}$ mice to examine the effects of pericyte deficiency on white matter integrity, and more specifically, in the corpus callosum. Our data show that pericyte deficiency leads to early BBB leakage, which precedes demyelination and axonal degeneration; at very early stages in adulthood (4wks old) animals present accumulation of blood byproducts (IgG and fibrin), however they show no defects in myelin and axonal integrity yet. Adult *Pdgfrβ*$^{F7/F7}$ mice (12-16wks old) exhibit a decrease in myelin thickness, as shown by electron microscopy, and a reduction in axonal and myelin-related protein expression, both of which deteriorate with aging. Furthermore, these animals exhibit behavioral deficits related to white matter damage. Previous studies have shown that hypoxia can

induce coagulation and thus the formation of fibrin deposits, events that are responsible for oligodendrocyte death. Our in vitro oligodendrocyte studies show that fibrin accumulation causes autophagy-induced mature oligodendrocyte death, hence implying that the events following BBB leakage are responsible for myelin destruction. To strengthen our results, we show that fibrinogen depletion can restore myelin integrity and reverse axonal damage. Taken together, our results show that pericyte deficiency causes BBB leakage at very early stages, followed by myelin destruction and axonal degeneration, thus emphasizing the importance of the neurovascular unit in health and disease.

Disclosures: A.M. Nikolakopoulou: None. **A. Montagne:** None. **Z. Zhao:** None. **A.P. Sagare:** None. **D. Lazic:** None. **Y. Wang:** None. **B.V. Zlokovic:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.12/N4

Topic: B.12. Demyelinating Disorders

Support: The Wellcome Trust Grant 110138/Z/15/Z
Department for the Economy Studentship

Title: The expression and role of CCN3 during central nervous system development and remyelination

Authors: *N. DE LA VEGA GALLARDO[1], R. G. PENALVA[1], J. FALCONER[1], J. MOFFAT[1], M. NAUGHTON[1], Z. LIN[2], B. PERBAL[3], R. INGRAM[1], D. C. FITZGERALD[1]
[1]Queen's Univ. Belfast, Belfast, United Kingdom; [2]Emory Univ. Sch. of Med., Atlanta, GA; [3]Univ. Côte d'Azur, Nice, France

Abstract: Multiple sclerosis is a demyelinating disease of the central nervous system (CNS) usually diagnosed in young adults and is characterised by immune-mediated destruction of myelin-producing oligodendrocytes. Whereas there is a plethora of disease modifying therapies to reduce relapses, there are currently no available treatments to boost myelin repair. Regulatory T cells (Treg) are necessary for murine remyelination to occur efficiently *in vivo*. Treg-secreted CCN3 promotes oligodendrocyte differentiation and developmental myelination in murine brain slice cultures and is expressed in both the rodent and human brain. These findings identify CCN3 as a candidate of interest in CNS development and regeneration and therefore we aim to investigate the expression and role of CCN3 during these processes.
CCN3 was detected in murine CNS tissue at a range of ages during postnatal development of C57BL/6 mice. CCN3 did not co-localise with $GFAP^+$ astrocytes or $Olig2^+$ cells of the oligodendrocyte cell lineage but did co-localise with NeuN, identifying neurons as the main

source of CCN3 in these studies. Major sites of CCN3 expression in the forebrain included the cerebral cortex, hippocampus and the suprachiasmatic nuclei. To investigate CCN3 expression during demyelination and remyelination, 11 week old, C57BL/6, male mice were fed with the demyelinating agent cuprizone. In addition to described CCN3 expression patterns in healthy adults, CCN3 was also detected in the septal nuclei during demyelination as well as concurrent and subsequent remyelination. To date, it is unknown whether CCN3 is actively involved in myelin regeneration in this model or whether this expression was a response to stress. Furthermore, the cellular or structural source of this CCN3 is currently unknown and under investigation. To study the role of CCN3 in spinal cord remyelination, 10 week old, $CCN3^{-/-}$ and $CCN3^{+/+}$, male mice were injected with lysolecithin toxin in the ventral white matter of the spinal cord. Crucially, there was no difference in the mean lesion size between genotype groups. This demonstrates a comparable burden of damage to resolve in these groups, validating this as a suitable system to study the effects of CCN3 on oligodendrocyte differentiation and remyelination in the spinal cord *in vivo*. Ongoing work is examining whether CCN3 is required for efficient remyelination in the CNS, and whether lack thereof affects myelin wrapping both in the brain and spinal cord. These studies could hold promise for the development of CNS regenerative therapeutics as well as advancing knowledge in the fields of myelin biology and CCN proteins.

Disclosures: N. De La Vega Gallardo: None. **R.G. Penalva:** None. **J. Falconer:** None. **J. Moffat:** None. **M. Naughton:** None. **Z. Lin:** None. **B. Perbal:** None. **R. Ingram:** None. **D.C. Fitzgerald:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.13/N5

Topic: B.12. Demyelinating Disorders

Support: IZKF Wuerzburg

Title: Revealing the pathogenesis of contactin-1 autoantibodies in inflammatory neuropathies

Authors: *J. GRUENER[1], C. VILLMANN[2], C. L. SOMMER[1], K. DOPPLER[1]
[1]Dept. of Neurol., Univ. of Wuerzburg, Wuerzburg, Germany; [2]Inst. for Clin. Neurobio., Univ. Wuerzburg, Wuerzburg, Germany

Abstract: Background and Objective:
Contactin-1 is a glycosylphosphatidylinositol (GPI)-anchored neuronal surface glycoprotein, which is located at the axonal side of the paranode and belongs to the immunoglobulin superfamily. The protein interacts with the contactin associated protein 1 (Caspr) on the axonal

side and with neurofascin-155 (NF155) on the glial side of the nerve fiber. The complex of these three proteins is required for the proper formation of the paranodal junction, which separates nodal voltage-gated sodium channels from juxtaparanodal voltage-gated potassium channels. In the last few years, autoantibodies to contactin-1 have been reported in some patients with inflammatory neuropathies. They all showed common clinical features like acute symptom onset, predominantly motor involvement and relapsing-remitting disease progression. This form of neuropathy is often associated with sensory ataxia and tremor. As binding of autoantibodies to dorsal root ganglia (DRG) neurons may cause sensory ataxia, we investigated the effects of contactin-1 autoantibodies on sodium currents of DRG neurons in order to study their pathogenesis.

Methods:

Primary neurons were isolated and cultivated from DRGs of adult mice. After one day in culture, currents of voltage-gated sodium channels were measured by patch clamp recordings in a whole-cell configuration mode. Following an incubation of the DRG neurons with serum of patients harboring autoantibodies to contactin-1 in comparison to serum of healthy controls, effects of this treatment on sodium currents were analyzed. Performing immunocytochemical stainings after each measurement ensured the binding of patients' autoantibodies to the primary neurons.

Results:

Immunocytochemistry showed strong and specific binding of patients' autoantibodies to DRG neurons. By contrast, no specific binding to DRGs was detected in binding assays with sera of healthy controls. Regarding electrophysiological measurements, first results indicate that DRGs which were treated with serum of patients who harbor autoantibodies to contactin-1 show lower sodium current densities in comparison to neurons which were incubated with serum of healthy controls.

Conclusions:

Preliminary results showed decreased sodium currents of DRG neurons that were treated with autoantibodies to the neuronal surface protein contactin-1. This indicates a pathogenic effect of the autoantibodies. In summary, our data will help to understand the biological mechanism of contactin-1 autoantibodies in patients with inflammatory neuropathies.

Disclosures: J. Gruener: None. **C. Villmann:** None. **C.L. Sommer:** None. **K. Doppler:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.14/N6

Topic: B.12. Demyelinating Disorders

Support: NIH R21NS093487
National Multiple Sclerosis Society grant RG1703

Title: Glial cell responses in CNS demyelination and myelin repair

Authors: *G. SAMTANI[1], D. R. MICHAUD[2], K. KONGANTI[3], S. J. KIM[2], J. LI[2]
[1]Texas A&M Inst. for Neurosci., College Station, TX; [2]Dept. of Vet. Integrative Biosci., Texas A&M Univ., College Station, TX; [3]Texas A&M Inst. for Genome Sci. and Society, College Station, TX

Abstract: Myelin, the lipid-enriched sheath enwrapping axons, is critical for the normal function of the nervous system. Loss of myelin or myelin-producing oligodendrocytes in the central nervous system (CNS) contributes to neurological disorders and age-related neurological decline. The promotion of remyelination and axon protection via oligodendrocyte precursors in the adult CNS presents an attractive therapeutic strategy, as these cells persist throughout the lifespan. However, our understanding of the myelin repair process after a demyelinating insult remains limited. In this study, we utilized an autoimmune-independent experimental mouse model of CNS demyelination to investigate glial cell functions during myelin repair. To facilitate direct visualization of myelin, transgenic mice expressing membrane-anchored EGFP in mature oligodendrocytes (CNP1-mEGFP) were used. Adult mice were fed 0.2% cuprizone diet for 2, 5, and 12 weeks, representing the early, acute, and chronic phases of demyelination. Remyelination was investigated in mice returned to normal diet for 1-2 weeks after 5 weeks of cuprizone intoxication or 4-8 weeks after 12 weeks of intoxication. Cuprizone intoxication induced oligodendrocyte apoptosis, microglial activation, astrogliosis and demyelination in a temporal and spatial fashion in the adult brain. After cuprizone withdrawal, spontaneous remyelination ensues rapidly after acute demyelination. Although remyelination was less efficient after chronic demyelination, significant remyelination was achieved following 4-8 weeks of recovery in both the corpus callosum (CC) and cortex. Myelin debris, determined by neural lipid staining, was abundant in chronic demyelinating lesions and disappeared as remyelination progressed. Immunohistochemical analysis revealed many autophagy conjugate LC3-II-decorated vesicles in the CC after chronic demyelination. While some LC3-II vesicles were EGFP+ and colocalized to microglia, many were not and were EGFP-, suggesting aberrant autophagy activities in axons. Immunostaining of non-phosphorylated Neurofilament H showed significant axonal damage that persisted even after 8 weeks of recovery. Transcriptome profiling of the corpus callosum at early phases of demyelination and remyelination revealed activation of multiple immune and signaling pathways, including extracellular matrix, actin cytoskeleton remodeling, and cell adhesion for myelin repair. Together, our data demonstrate dynamic glial responses during demyelination and remyelination, and also suggest that persistent axonal damage due to chronic demyelinating insults may underlie remyelination failure.

Disclosures: G. Samtani: None. **D.R. Michaud:** None. **K. Konganti:** None. **S.J. Kim:** None. **J. Li:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.15/N7

Topic: B.12. Demyelinating Disorders

Support: NINDS Grant 1R01NS081141-01A1
NMSS Pilot Grant RG-NMSS (NCE)

Title: Remodeling of GABAergic innervation may contribute to cortical hyperexcitability and seizures in chronically demyelinated mice

Authors: *A. S. LAPATO[1], C. R. JONAK[2], K. LAUDERDALE[2], D. K. BINDER[3], S. K. TIWARI-WOODRUFF[4]
[1]Univ. of California Riverside Sch. of Medic, Riverside, CA; [2]Univ. of California Riverside, Riverside, CA; [3]Univ. of California Riverside Div. of Biomed. Sci., Riverside, CA; [4]Univ. of California Riverside Sch. of Med., Riverside, CA

Abstract: Background Epileptic seizures are estimated to be up to six-fold more prevalent among multiple sclerosis (MS) patients than the population overall. However, while seizures are more common in MS patients and predict significant morbidity & mortality, epileptogenesis in MS remains poorly understood. Objective To identify functional and cytoarchitectural changes potentially etiologic to demyelination-induced seizures using the cuprizone (CPZ) diet model of MS. Methods 8-week-old male C57BL/6 mice were fed 12 weeks of 0.2% CPZ diet (12wkCPZ; n=8) or standard chow (normal; n=7). *Multielectrode array (MEA) EEG:* 30-channel MEA probes were positioned bilaterally over the dorsal surface of the skull and oscillation frequency power was analyzed. *Immunohistochemistry:* myelination, axon pathology, and GABAergic cells were assessed in sagittal sections at ~ ML +1.5 mm. *Electrophysiology:* field inhibitory postsynaptic currents (fIPSCs) were recorded in the presence of NBQX and AP5. Results 12wkCPZ mice displayed generalized seizures and increased EEG power vs normal mice. Medial areas demonstrated the most dramatic increase across multiple frequency bands and was the only cluster to exhibit greater power in the 30-100 Hz range. Along with significant loss of myelin, SMI-32+ varicosities were observed in commissural fiber tracts. Cortical GAD65/67+ area was reduced in 12wkCPZ mice, while GAD65/67+ staining was increased in rostral white matter, suggesting GABAergic remodeling. 12wkCPZ mice displayed numerous parvalbumin (PV)+ projections between the cortex and striatum that were not seen in normal mice. Cortical fIPSCs were reduced in slices from 12wkCPZ mice while stimulation of striatal PV+ projection fibers evoked altered fIPSCs in 12 wk CPZ mice. Conclusions Neural excitability, pathology of white matter commissural axons, plasticity of PV+ innervation, and aberrant GABAergic transmission between cortical and subcortical areas likely contribute to demyelination-induced

seizures. Planned longitudinal MEA recordings will help expose pathophysiology leading to initiation of seizures and its associated changes to regional connectivity, remodeling of inhibitory circuitry, and attending cellular/molecular substrates.

Disclosures: A.S. Lapato: None. **C.R. Jonak:** None. **K. Lauderdale:** None. **D.K. Binder:** None. **S.K. Tiwari-Woodruff:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.16/N8

Topic: B.12. Demyelinating Disorders

Title: Cortical cell-type differences at baseline in the presence of Cx deficiency

Authors: *S. KEIL[1], M. FREIDEN[1], C. ABRAMS[2]
[2]Neurol. and Rehabil., [1]Univ. of Illinois Chicago, Chicago, IL

Abstract: Glial cells of the central nervous system (CNS) express several different connexins (Cx). These connexins are integral membrane proteins that form gap junction channels and provide a low resistance pathway for the diffusion of small molecules and ions between coupled cells. The mutation or deficiency of oligodendrocytic Cx32 and Cx47 has been linked to the disease states X-linked Charcot-Marie-Tooth disease (CMT1X) and Pelizaeus-Merzbacher-Like disease 1 (PMLD1), respectively. With recent data suggesting this deficiency effects both inflammatory and immune response pathways, this experiment investigates how the disruption of Cx32 and Cx47 effects the central nervous system, with the goal of parsing out potential differences in microglial populations. Utilizing immunolabeling we examined presence of oligodendrocytes, astrocytes and microglia in Cx32KO, Cx47KO, and mutant mice when compared to wild-type controls. The results continue to support and highlight the critical role connexins play within the central nervous system and implicates further investigation into therapeutic targets.

Disclosures: S. Keil: None. **M. Freiden:** None. **C. Abrams:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.17/N9

Topic: B.12. Demyelinating Disorders

Title: Region specific changes in gliosis following reduced extracellular vesicle release in the twitcher mouse model of Krabbe disease

Authors: *C. R. REITER[1], D. WOZNIAK[3], J. MARSHALL[2], G. SCESA[2], I. GIVOGRI[2], E. R. BONGARZONE[2]
[1]Med. Scientist Training Program, [2]Anat. & Cell Biol., Univ. of Illinois at Chicago, Chicago, IL; [3]Aurora Univ., Aurora, IL

Abstract: Here we have studied the potential of extracellular vesicles (EVs) released within the Twitcher mouse brain to induce pathology, considering whole brain cellular interactions and individual cell type contributions. Krabbe Disease (KD) is a monogenetic lysosomal storage disorder caused by mutations in the gene encoding galactosylceramidase (GALC). Loss of this lysosomal enzymatic activity causes accumulation of a toxic sphingolipid, galactosylsphingosine (psychosine). Accumulation of psychosine has long been hypothesized to drive the observed pathology in KD patients, which includes oligodendrocyte and Schwann cell cytotoxicity, astrogliosis, microglial activation and the presence of abnormal globoid cells throughout diffusely demyelinating white matter. Extracellular vesicles (EVs) are secreted by most all mammalian cells to facilitate intercellular communication in healthy and pathologic states. Release of vesicles occurs by traditional exocytotic machinery (exosomes) or membrane shedding events (microvesicles). EVs have been shown to provide a vast array of communication signals via membrane proteins and lipids, as well as nucleic acid cargos such as microRNA. We have found EVs with elevated levels of psychosine in the Twitcher (Twi) mouse model of KD; this study aims to understand the pathologic role of psychosine-laden EVs. We hypothesize that EVs contribute to the observed pathology in KD by two intertwined mechanisms; vesicular release serves as a mechanism to preserve individual cell survival by unloading excess lipid, and these EVs induce pathology in distant cells through the spread of psychosine toxicity. To test these hypotheses, we optimized a treatment regimen utilizing a Sphingomyelinase 2 inhibitor (GW4869), which has been demonstrated to reduce exosome and microvesicle release by depleting ceramide pools. The inhibitor or DMSO vehicle were injected intraperitoneally every other day from postnatal day (P) 10 until P20 or P40 in 6 total mice per treatment group, each comprised of 3 males and 3 females. Disease scores were tracked during the treatment period and showed increased severity in treated mice. EV populations were reduced in treated mice and consequently more psychosine was associated with cellular fractions. Immunohistochemical analysis identified region specific increases in astrocytosis and microglial activation. *In vitro* cultures of each glial subtype have been established to determine which cellular populations release and/or receive EVs. These findings will elucidate which cell types lead to psychosine-induced pathology and highlight the contributions of vesicles to observed cytotoxicity.

Disclosures: C.R. Reiter: None. **D. Wozniak:** None. **J. Marshall:** None. **G. Scesa:** None. **I. Givogri:** None. **E.R. Bongarzone:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.18/N10

Topic: B.12. Demyelinating Disorders

Support: MIUR, PON 'Ricerca e Competitività 2007 - 2013' project PON01_02512
Regione Veneto project protocol 103173COF/14/LR52001C2/000051

Title: A co-ultramicronized palmitoylethanolamide/luteolin composite mitigates clinical disability score and disease-relevant molecular markers in a mouse model of experimental autoimmune encephalomyelitis

Authors: *S. D. SKAPER, G. CONTARINI, L. FACCI, M. BARBIERATO, D. FRANCESCHINI, M. ZUSSO, P. GIUSTI
Pharmaceut. & Pharmacol. Sci., Univ. of Padua, Padua, Italy

Abstract: Multiple sclerosis (MS) is the prototypical inflammatory disease of the CNS, whose defining feature is destruction of myelin. MS is the most frequent cause of chronic neurological impairment in young people. The autoimmune nature of the disease has led to the development of therapeutic strategies based on immunosuppressants, immunomodulators, and monoclonal antibodies. In spite of the noteworthy gains in treating MS, these agents do not necessarily ensure repair or target oligodendrocytes (OLs), the myelin-producing cells of the CNS. MS lesions are characterized by a pool of undifferentiated oligodendrocyte precursor cells (OPCs) which fail to mature into myelin-producing OLs. A co-ultramicronized composite of N-palmitoylethanolamine (PEA) and the flavonoid luteolin (co-ultraPEALut, 10:1 by mass), which possesses analgesic, anti-inflammatory, and neuroprotective is efficacious in improving outcome in several CNS injury models. Co-ultraPEALut also promotes OPC differentiation in vitro. Experimental autoimmune encephalomyelitis (EAE), based on active immunization with myelin oligodendrocyte glycoprotein (MOG35-55) in female C57BL/6 mice was used to study the effects of co-ultraPEALut on clinical outcome and expression of disease-relevant markers. Co-ultraPEALut, given intraperitoneally daily starting on day 11 post-immunization (initiation of disease onset) dose-dependently improved clinical score over the range 0.1-5 mg/kg. Cerebellar signs/symptoms and cognitive dysfunction contribute to MS clinical disability. Further, medulla oblongata volume is considered a valid biomarker of spinal cord damage/disability in MS. For gene expression profiling in medulla oblongata and cerebellum, mice were treated daily with 5 mg/kg co-ultraPEALut starting the second day post-immunization. We observed time-dependent increases over a 21-day period in markers for inflammation cytokines, chemokines, serum amyloid A, inducible nitric oxide synthase and the NLRP3 inflammasome, along with glial cell activation. Markers characteristic of immune system activation in MS (CD4, MCP-1, CD137)

were also elevated. Timing varied as a function of the gene studied, with values generally being low at 7 days, and either peaking at 14 days and/or remaining elevated through 21 days post-immunization. Treatment with co-ultraPEALut reduced the enhanced expression of a number of these genes. Strategies intended to promote remyelination in MS should focus on both enhancing long-term survival of OPCs and stimulating these cells to differentiate into remyelinating OLs. Within this context, co-ultraPEALut may represent a novel pharmacological approach.

Disclosures: S.D. Skaper: None. **G. Contarini:** None. **L. Facci:** None. **M. Barbierato:** None. **D. Franceschini:** None. **M. Zusso:** None. **P. Giusti:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.19/N11

Topic: B.12. Demyelinating Disorders

Support: National Multiple Sclerosis Society (Pilot clinical trial PR-1412-02135)
National Multiple Sclerosis Society (RG5203A4)
NIH/NINDS (R01NS062796)
NIH/NINDS (NS095889)
Rachleff Endowment to J.R.C
National Multiple Sclerosis Society (Career Transition Award TA 3062-A-3)

Title: Selective estrogen receptor modulators significantly enhance remyelination in an estrogen receptor-independent manner

Authors: *K. RANKIN[1,1], F. MEI[1], Y.-A. SHEN[1], S. R. MAYORAL[1], C. DESPONTS[2], D. LORRAIN[2], C. CORDANO[1], S. BARANZINI[1], A. GREEN[1], J. R. CHAN[1], R. BOVE[1]
[1]Univ. of California San Francisco, San Francisco, CA; [2]Inception Sci., San Diego, CA

Abstract: Multiple Sclerosis is a neurologic disease characterized by widespread demyelination with subsequent degeneration of axons. Remyelination of these axons has been widely proposed as a key therapeutic target to reverse clinical disability associated with disease progression. Utilizing the screening technique binary indicant for myelination using micropillar arrays (BIMA), we identified selective estrogen receptor modulators (SERMs) as a cluster that enhances oligodendrocyte precursor cell (OPC) differentiation and subsequently promotes remyelination. In particular, we have identified Bazedoxifene (BZA) as a potent agent of OPC differentiation and subsequent remyelination. BZA stands out, as not only is it FDA-approved, but has proven extremely tolerable in clinical trials.
When administered to both human and rat OPCs, BZA significantly enhanced OPC differentiation *in vitro*. In co-cultures, BZA promoted OPC differentiation and myelination of

axonal substrates. Across multiple models of demyelination, we found that BZA significantly enhanced remyelination and accelerated the kinetics of repair. As a SERM, BZA was developed to differentially agonize/antagonize the nuclear estrogen receptors α and β (ERα and ERβ). Based on conflicting results of various SERMs on OPC differentiation, we sought to validate BZA's target. To this end, OPCs from total ERα and ERβ knockouts, as well as double ER-knockouts were isolated and cultured. We measured significantly enhanced OPC differentiation across all knockout models, suggesting that in contrast to the existing literature, nuclear ERs are not necessary for BZA, as well as other SERMs, to promote differentiation. In a focal demyelination model in wild-type and ER-double knockout mice, all mice treated with BZA displayed significant improvements in remyelination when compared with vehicle-treated mice. Using an exciting new bioinformatics method, we have identified potential candidate targets for SERMs' robust effects on OPC differentiation and remyelination, and work to narrow down the receptor is well underway.

Disclosures: K. Rankin: None. **F. Mei:** None. **Y. Shen:** None. **S.R. Mayoral:** None. **C. Desponts:** None. **D. Lorrain:** None. **C. Cordano:** None. **S. Baranzini:** None. **A. Green:** None. **J.R. Chan:** None. **R. Bove:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.20/N12

Topic: B.12. Demyelinating Disorders

Support: HMRF 05162936

Title: Overcoming CSPG-mediated inhibition of remyelination by targeting PTPσ in experimental models of multiple sclerosis

Authors: *S. R. BADEA[1], H. SUN[2,4], J. HUANG[1,3], W. WU[5,1]
[1]Sch. of Biomed. Sci., The Univ. of Hong Kong, Hong Kong, Hong Kong; [2]Sch. of Biomed. Sci., The Univ. of Hong Kong, Hong Kong SAR, China; [3]State Key Lab. of Brain and Cognitive Sci., The Univ. of Hong Kong, Hong Kong, Hong Kong; [4]Zhujiang Hosp. Dept. of Neurosurg., Southern Med. Univ., Guangzhou, China; [5]GHM Inst. of CNS regeneration, Jinan Univ., Guangzhou, China

Abstract: Introduction: Changes in chondroitin sulphate proteoglycans (CSPGs) following neural injury or as part of a neurodegenerative process lead to the inhibition of myelin repair**.** Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by inflammation-induced destruction of the myelin sheath that surrounds axons, with focal demyelinated lesions distributed across multiple locations throughout the CNS. In MS,

CSPGs are deposited at the border of active and expanding demyelinating lesions, and may create a barrier for migration and repopulation by oligodendrocyte progenitor cells (OPCs). CSPG inhibition of axonal regeneration is partially mediated by the protein tyrosine phosphatase sigma (PTPσ) receptor. PTPσ is also the main player of CSPG inhibition of oligodendrocyte (OL) outgrowth and myelination. Intracellular sigma peptide (ISP), a newly developed membrane permeable peptide binds to PTPσ and relieves CSPG-mediated inhibition has been used to promote regeneration after spinal cord injury. Identification of PTPσ as a functional receptor for CSPGs in oligodendrocytes presents a promising avenue of investigation to rescue OL activity and promote recovery in demyelinating lesions.
Aim: We hypothesize that *in vitro* CSPG-mediated inhibition of OPCs can, at least partially, be overcome by blocking receptor PTPσ, leading to improved remyelination and functional recovery.
Methods: OL precursor cells were seeded on coverslips spotted with CSPGs. Cytotoxicity was determined using LDH assay, whereas proliferation was quantified by population doubling. Different stages of the oligodendroglial lineage, as well as CSPG presence, OL migration in the inhibitory zone and PTPσ expression, were determined using immunocytochemistry. Experimental autoimmune encephalomyelitis was induced in female C57BL/6J mice and functional recovery was assessed following daily ISP (10μM) injection over 28 days. Remyelination was assessed by histological staining and electron microscopy.
Results: ISP did not cause significant cell death, but at higher concentrations affected cell adhesion and led to cell detachment. Proliferation and differentiation were not inhibited. ISP treatment of OPCs led to increased migration and proliferation in the CSPG-coated areas. ISP-treated mice showed a decreased microglial presence, reduced cellular infiltrates and increased remyelination and functional recovery, without influencing the expression of CSPGs.

Disclosures: S.R. Badea: None. **H. Sun:** None. **J. Huang:** None. **W. Wu:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.21/O1

Topic: B.12. Demyelinating Disorders

Support: NMSS RG 4853A3/2
NIH R01 NS081141-01A1

Title: Diffusion tensor imaging can identify aspects of therapeutic estrogen receptor beta ligand-induced remyelination in a mouse model of multiple sclerosis

Authors: *K. ATKINSON[1], J. LEE[2], S. KIM[4], A. DREW[2], J. HASSELMANN[5], J. S. SOTO[6], N. G. HARRIS[7], A. OBENAUS[3], J. KATZENELLENBOGEN[4], S. K. TIWARI-WOODRUFF[1]

[1]Univ. of California, Riverside, Riverside, CA; [3]Dept Pediatrics, [2]Loma Linda Univ., Loma Linda, CA; [4]Univ. of Illinois at Urbana-Champaign, Champaign, IL; [5]Univ. of California, Irvine, Irvine, CA; [6]Neurosci., [7]Neurosurg., UCLA, Los Angeles, CA

Abstract: Diffusion tensor imaging (DTI) can detect white matter microstructural changes, the pathological nature of which can be validated by histological assessments. As most clinical trials use brain imaging parameters to assess therapeutic success, we wanted to investigate the ability of DTI to resolve remyelination and neuroprotection following estrogen receptor β ligand Indazole chloride (Ind-Cl) treatment in the cuprizone (CPZ) diet model of MS. Adult C57BL/6J male and female mice received 9 weeks of normal diet (normal), 9 weeks CPZ diet (9wkDM), 9 weeks CPZ with 2 weeks normal diet + vehicle (RM+V), or 9 weeks CPZ with 2 weeks normal diet + Ind-Cl (RM+Ind-Cl). *In vivo* and *ex vivo* DTI data were acquired to derive quantitative tissue microstructure measures in the corpus callosum (CC). Fractional anisotropy (FA), axial and radial diffusivity (AD and RD) were compared to immunohistochemistry (IHC). A decrease in FA and an increase in RD, but not AD in DM groups was observed in both *in vivo* and/or *ex vivo* DTI as compared to normal mice. An increase in FA and a decrease in AD and RD was observed in RM+Ind-Cl as compared to RM+V groups reflective of remyelination and improved axonal health only *ex vivo*. In conclusion, DTI imaging is sensitive to demyelination and remyelination and can serve as a valuable translational tool to assess MS pathophysiology. However, standard DTI acquisitions may not be sufficiently sensitive to measure demyelination and remyelination changes as observed with immunohistochemistry, necessitating the utilization of advanced imaging methods.

Disclosures: J. Lee: None. **S. Kim:** None. **A. Drew:** None. **J. Hasselmann:** None. **J.S. Soto:** None. **N.G. Harris:** None. **A. Obenaus:** None. **J. Katzenellenbogen:** None. **S.K. Tiwari-Woodruff:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.22/O2

Topic: B.12. Demyelinating Disorders

Support: Seed Grant from the BICP

Title: 'Effects of ketogenic diet and ketone esters on remyelination in cuprizone/rapamycin model of demyelination'

Authors: *N. ALAEIILKHCHI[1], K. L. KOLEHMAINEN[2], O. SEIRA[3], A. J. MOULSON[4], W. TETZLAFF[5]
[1]Intl. Collaboration on Repair Discoveries, Vancouver, BC, Canada; [2]Univ. of British Columbia,

Vancouver, BC, Canada; [3]ICORD/UBC, Vancouver, BC, Canada; [4]Intl. Collaboration On Repair Discoveries, Vancouver, BC, Canada; [5]Univ. of British Columbia, ICORD, Vancouver, BC, Canada

Abstract: Multiple sclerosis (MS) is characterized by demyelination and axonal injury/degeneration. Demyelinated axons are thought to be more susceptible to degeneration, due to exposure to the inflammatory environment and metabolic stress. Promoting remyelination therefore is a promising therapy, as it might mitigate axonal loss. As opposed to pharmacological therapies, diet-based treatments have fewer side-effects. Ketogenic diet (KD) (high in fat, adequate in protein, while very low in carbohydrates) increases ketone body production and decreases inflammation, which is thought to facilitate remyelination. KD is currently being used clinically for some treatment-resistant epilepsy, but its efficacy in MS models is unknown. Our objective is to assess the effects of KD on remyelination efficacy and oligodendrocyte differentiation in the cuprizone/rapamycin (cup/R) model of demyelination. We hypothesize that KD will promote oligodendrocyte differentiation and increase remyelination as compared to standard diet (SD). We bred transgenic mice carrying membrane-bound green fluorescent protein (mGFP) under the tamoxifen-inducible platelet-derived growth factor receptor α (PDGFRα) promoter (PDGFRα-CreER^{T2}::ROSAmT/mG) (to label new myelin). Demyelination was induced by feeding the mice 0.3% cuprizone (in the diet) for 6 weeks which was accompanied by rapamycin injections 5 times a week (6w-cup/R). The treatment group received ketogenic diet (KD) throughout, while the control group received standard diet (SD). Rotarod behavioral analysis was conducted throughout. Animals were sacrificed at 9 days after cessation of 6w-cup/R and immunohistochemical analysis was conducted. KD improved rotarod recovery and caused an increase in CC1 expression (indicative of increased oligodendrocyte differentiation). Tissue samples are currently being analyzed for new myelination (i.e. mGFP+ sheaths) and myelin pathology (i.e. demyelination, myelin decompaction, etc.) as well as mitochondrial function and axonal survival.

Disclosures: N. Alaeiilkhchi: None. **K.L. Kolehmainen:** None. **O. Seira:** None. **A.J. Moulson:** None. **W. Tetzlaff:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.23/O3

Topic: B.12. Demyelinating Disorders

Support: Vetenskapsrådet

Title: Overexpression of glutathione S transferase 4 alpha regulates OPC proliferation, differentiation and their capacity to remyelinate

Authors: *K. CARLSTROM, F. PIEHL, 17176
Dept. of Clin. Neurosci., Stockholm, Sweden

Abstract: Demyelination is a process in which axon-surrounding myelin is lost due to genetic, toxic or inflammatory mechanisms. In Multiple sclerosis (MS), this is a cause of an autoimmune reaction against the myelinating oligodendrocytes. Following degradation of myelin, oligodendrocyte precursor cells (OPCs) will differentiate into myelin producing cells and remyelinate intact axons. Glutathione S transferase 4 alpha (Gsta4) have an essential role in clearance of 4-hydroxynonenal (HNE), a highly reactive and toxic aldehyde. HNE is generated from unsaturated lipids during oxidative stress, where oligodendrocytes are particularly vulnerable due to their high lipid content and the increased oxidative pressure during their differentiation and remyelination. In this study we have examined the effect of introducing an overexpression construct containing the Gsta4 gene. We show that Gsta4 will influence downstream genes involved in oligodendrocyte differentiation and regulate differentiation of OPCs *in vitro*. We show that Gsta4 is also important in a clinically relevant disease model of MS; experimental autoimmune encephalomyelitis, where overexpressing animals recover faster and show less demyelination in spinal cord compared to wt. Further, we detected greater number of differentiated oligodendrocytes in Gsta4 overexpressing animals compared to wt after lysolecithin injections, causing transient demyelination in the corpus callosum. No differences in OPC proliferation were seen. Histological and electron microscopy analysis after injections confirmed a higher degree of remyelination in overexpressing animals versus wt. Phenotyping with RNAseq of intermediate oligodendrocytes suggest crucial signaling pathways are affected by Gsta4 and levels of HNE. As an example Gsta4 overexpressing OPCs have altered Wnt-signaling key players such as Axin2 and Tankyrase, suggesting that they are more prone to differentiate compared to wt OPCs. In conclusion, we provide evidence that Gsta4 and oxidative mechanisms could be of importance for OPCs' capacity to proliferate, differentiate and for their ability to remyelinate, both in an inflammatory and non-inflammatory disease model.

Disclosures: K. Carlstrom: None. **F. Piehl:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.24/O4

Topic: B.12. Demyelinating Disorders

Support: NIH Grant R21NS100000-01A1

Title: Loss of Schwann cell connexin32 regulates iNOS and tyrosine nitration

Authors: *M. FREIDIN[1], F. QARNI[2], C. K. ABRAMS[3]
[1]Neurol., Univ. of Illinois At Chicago, Chicago, IL; [3]Neurol. & Rehabil., [2]Univ. of Illinois at Chicago, Chicago, IL

Abstract: X-linked Charcot–Marie–Tooth disease (CMT1X) is an inherited peripheral neuropathy associated with mutations in GJB1, the human gene for Connexin32 (Cx32). Defects in gap junction communication alone does not appear to fully account for the role of Cx32 in myelinating glial cells. Recent studies demonstrate roles for connexins in the regulation of cell growth, apoptosis, and cellular stress signaling that are independent of functional gap junction channels. Microarray studies from our lab comparing gene expression in sciatic nerves from wild-type (WT) and Cx32-knockout (Cx32KO) identified significant regulation of genes in the mitochondrial inflammatory/stress pathways. Preliminary data show elevation of NO and mitochondrial stress in Cx32KO Schwann cells (SCs) compared to WT along with increases in downstream protein (tyrosine) nitration. We hypothesize that loss or mutation in Cx32 predisposes SCs to dysregulation of mitochondrial stress pathways, resulting in activation of nitric oxide. We examined the regulation and relative levels of NOS isoforms (NOS1-3) in WT and Cx32KO SCs and sciatic nerves. NOS2 (iNOS) levels were increased in Cx32KO samples, along with labeling for nitro-tyrosine (nitro-Tyr). Cx32 has been shown to confer resistance to cellular injury and cell death under toxic conditions where gap junctions played no part. Stimulation of cellular stress by treatment with H2O2 upregulated iNOS and nitro-Tyr in WT but had limited effects in Cx32KO SCs; further suggesting that loss or disruption of Cx32 activates a self-reinforcing positive feedback loop involving dysregulation of NOS and mitochondrial stress pathways.

Disclosures: M. Freidin: None. **F. Qarni:** None. **C.K. Abrams:** None.

Poster

653. Demyelinating Disorders: Molecular and Cellular Mechanisms: Therapeutics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 653.25/O5

Topic: B.12. Demyelinating Disorders

Support: MDA

Title: Involvement of astrocyte monocarboxylate transporter 1 in mouse models of demyelination

Authors: *T. PHILIPS[1], J. D. ROTHSTEIN[2]
[1]Dept. of Neurology, Brain Sci. Inst., [2]Brain Sci. Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: In the CNS, astrocytes provide trophic support to neighboring neurons, eg by ion and glutamate buffering and promoting axonal outgrowth during neuronal development. Upon neuronal injury, astrocytes become ‘reactive’: they express a whole plethora of neuro-immunomodulatory factors that will either have benign or detrimental influences on the surrounding neurons. One of the trophic functions exerted by astrocytes is the release of lactate through so-called monocarboxylate transporters (MCTs) of which MCT1 and MCT4 are expressed by astrocytes. MCTs allow the transfer of lactate from cells to the extracellular space from which neurons can take up lactate through their MCT subtype MCT2. Neurons will then use lactate as an energy metabolite to fuel their own ATP demands. It has been suggested that this astrocyte derived lactate is essential for long term memory formation in rats and could promote recovery upon ischemic injury in mice. In these studies, the true glial source of lactate remained elusive as lactate could also be provided by other glial cells. In fact, a role for MCT1 in oligodendrocytes has been suggested as loss of oligodendrocyte MCT1 leads to axonal injury. In order to fully understand the cell specific importance of MCT1 under normal physiological conditions as well under conditions of CNS injury, we have generated conditional MCT1 null mice in which MCT1 exon2 is inserted in between two loxP sites. Upon crossing with GFAP-Cre mice, we obtained very efficient knock-out of MCT1 specifically in astrocytes but not in oligodendrocytes or neurons. To our surprise, loss of MCT1 in astrocytes was well tolerated with no significant pathological or behavioral changes observed in these animals up to the age of one year. Motor skills as well as different learning skill paradigms were unaffected upon knock-out of MCT1 in astrocytes. Interestingly, MCT1 expression was significantly upregulated in mouse models of neuro-injury that were characterized by astrogliosis. MCT1 upregulation was not a consequence of non-specific upregulation of common astrocyte markers, eg GFAP, nor was it affected by a pro-inflammatory astrocytic reaction (A1-astrocytosis). Astrocyte MCT1 upregulation was concomitant with injury to the myelin sheath that enwraps axons to ensure fast action potential conduction. MCT1 upregulation was most notable during the late stages of demyelination while remyelination is ongoing. This striking upregulation of MCT1 in models of demyelination now sheds light on an exciting and novel role of MCT1 in neuro-injury, which could be a novel target for future oligodendrocyte and neuronal repair upon demyelinating injury.

Disclosures: T. Philips: None. **J.D. Rothstein:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.01/O6

Topic: C.03. Parkinson’s Disease

Support: NIH Grant UH3 NS100553-01

Michael J. Fox Foundation

Title: Hyperdirect pathway activation by DBS: An intraoperative ECoG study using paired pulses

Authors: *H. C. WALKER[1], M. AWAD[2], B. L. GUTHRIE[2], A. NAKHMANI[4], C. L. GONZALEZ[2], Z. T. IRWIN[3]
[1]Neurol., UAB, Birmingham, AL; [3]Neurol., [2]Univ. of Alabama at Birmingham, Birmingham, AL; [4]Electrical & Computer Engin., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Directional DBS shows great promise for Parkinson's disease (PD) and other neuropsychiatric disorders; however, the increased number of stimulation contacts greatly complicates device activation and adjustment. Our previous EEG findings suggest that DBS evokes both short and long latency neural oscillations in sensorimotor cortex and that different patterns of cortical activation might distinguish effective versus ineffective stimulation sites within an individual. Here we sought to spatially localize these potentials and validate their neural origin with electrocorticography (ECoG) during DBS surgery. In five PD subjects, we placed an ECoG strip across the central sulcus during subthalamic DBS surgery and delivered bipolar stimulation at therapeutic settings. Stimulation was delivered in paired pulses with 90 different inter-stimulus intervals ranging from 0.18 to 30 ms to examine the latency, spatial distribution, and absolute and relative refractory periods of putative cortical activation by DBS. Similar to prior EEG studies, we observed robust short (R1) and long latency (R2/R3) cortical activation over both M1 and S1. R1/R2/R3 collectively displayed absolute and relative refractory periods of 0.59 ± 0.20 ms and 1.70 ± 1.02 ms, respectively (mean ± SD). At our level of statistical power, there were no significant differences between M1 and S1 in R1 latency (0.43 ± 0.15 versus 0.60 ± 0.26 ms, p = 0.29, unpaired t-test) or amplitude (3.5 ± 1.9 versus 3.6 ± 3.8 μV, p = 0.98), though amplitudes were more consistent in M1 versus S1 across subjects. Similarly, there were no significant differences in R2/R3 onset latency (1.9 ± 0.6 versus 3.3 ± 2.4 ms; p = 0.30), but R2/R3 amplitude was significantly larger in M1 versus S1 (11.5 ± 5.9 versus 3.1 ± 2.6 μV; p = 0.04). Our ECoG findings validate the neural origin of cortical potentials elicited by STN DBS and suggest that they involve at least M1 and S1 ipsilateral to the DBS electrode. Stimulus-evoked activity shows considerable promise as a predictive biomarker to guide both directional and closed loop DBS and to better understand systems-level interactions between DBS and cortical motor circuits in humans.

Disclosures: M. Awad: None. **B.L. Guthrie:** None. **A. Nakhmani:** None. **C.L. Gonzalez:** None. **Z.T. Irwin:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.02/O7

Topic: C.03. Parkinson's Disease

Support: Medtronic, Inc

Title: Investigation of non-invasive predictors for outcome during DBS surgery for PD

Authors: *M. AWAD[1], C. L. GONZALEZ[2], A. NAKHMANI[3], Z. IRWIN[2], B. L. GUTHRIE[4], H. C. WALKER[2]
[1]Electrical Engin., Univ. of Alabama at Birmingham, Hoover, AL; [2]Neurol., [3]Electrical Engin., [4]Neurosurg., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Background: Although deep brain stimulation (DBS) improves motor symptoms, we lack fundamental knowledge about how it modulates brain circuits. Better understanding the electrophysiology of DBS could guide surgical targeting, postoperative programming, and closed loop stimulation. Our goal was to contrast stimulus-evoked electrophysiology elicited by subthalamic nucleus (STN) DBS at effective versus ineffective stimulation contacts, and to evaluate whether stimulus-evoked activity might serve as a biomarker to inform targeting during "asleep" DBS surgeries.
Materials and Methods: We examined event-related potentials (ERPs) elicited by STN DBS in 11 participants. As part of routine care, patients underwent electrode targeting while awake followed by pulse generator connection one week later under total intravenous anesthesia (TIVA). Stimuli were delivered in a randomized block design from the DBS lead during both surgical procedures with an external pulse generator with a range of voltages between 0 and 8.0 V in 0.5 V increments. ERPs were recorded using EEG electrodes placed on the scalp around the sterile field. Relevant clinical outcomes including UPDRS change and therapeutic window were correlated with the stimulus-evoked scalp electrophysiology.
Results: DBS elicits scalp ERPs regardless of the anesthesia state with both short (R1) and longer (R2 and R3) latency potentials. R1 was preserved to a greater extent under TIVA versus the later components of the response (R2 & R3). Regardless of anesthesia state, we found especially short R1 latencies at motor-adverse corticospinal tract stimulation sites (~500 μsec). Long latency responses under TIVA were often markedly attenuated (present in only 5/11 participants, 45.4%) or delayed (40.7 ± 1.0 versus 30.8 ± 0.7 ms, $t=7.87$, $p<0.001$) versus awake. Receiver operating characteristic (ROC) curves indicate that R1 latency can predict postoperative motor side effects versus sites without motor side effects (AUC = 83.6% awake and 75.6% under sedation).
Conclusions: Regardless of anesthesia state, DBS at adverse corticospinal / corticobulbar

stimulation sites elicits shorter latency R1 responses, whereas stimulation at clinically effective sites elicits more delayed, variable R1 timing. These findings suggest that stimulus evoked scalp electrophysiology can detect clinically meaningful interactions between DBS and specific motor sub-circuits within inidividuals. Given its resilience to sedation, short latency cortical activation shows promise as a predictive biomarker to guide DBS targeting under general anesthesia.

Disclosures: M. Awad: None. **C.L. Gonzalez:** None. **A. Nakhmani:** None. **Z. Irwin:** None. **B.L. Guthrie:** None. **H.C. Walker:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.03/O8

Topic: C.03. Parkinson's Disease

Support: NSF US IGNITE 10037840
NSF CAREER Award 1351112
NSF GRFP 1256065

Title: Anodic stimulation misunderstood: Application of anodic stimulation for preferential activation of fiber orientations in deep brain stimulation

Authors: *D. N. ANDERSON[1], G. DUFFLEY[2], J. VORWERK[3], A. D. DORVAL[2], C. R. BUTSON[3]
[2]Dept. of Bioengineering, [3]Scientific Computing & Imaging Inst., [1]Univ. of Utah, Salt Lake City, UT

Abstract: Classically, extracellular cathodic stimulation has been used in deep brain stimulation (DBS) for therapeutic benefit. It is widely agreed that cathodic stimulation causes activation of passing axons, however the role of anodic stimulation on activation of axons is less understood. We hypothesize that anodic stimulation can preferentially target neurons based on fiber orientation and anodic stimulation can be used for therapeutic benefit.
We used bioelectric field models and multicompartment NEURON models to explore preferential activation of neurons using anodic and cathodic stimulation. We explored neuron activation trends based on fiber orientation in a clinical scenario, DBS for Parkinson's disease. Tractography for the hyperdirect pathway, associated with clinical benefits, and internal capsule, associated with side effects, was generated using Diffusion Tensor Imaging (Fig. 1A).
We found that the hyperdirect pathway (oriented orthogonal to lead) was activated by anodic stimulation at lower thresholds than by cathodic stimulation. Activation thresholds of the internal capsule (vertically passing the lead) were increased with anodic stimulation (Fig. 1B). In this clinical scenario, anodic stimulation widened the therapeutic window of DBS as fiber pathways

associated with clinical benefit had 50% lower activation thresholds while activation thresholds for fiber pathways associated with side effects increased. Anodic stimulation preferentially activates fibers approaching or leaving the electrode at lower thresholds.

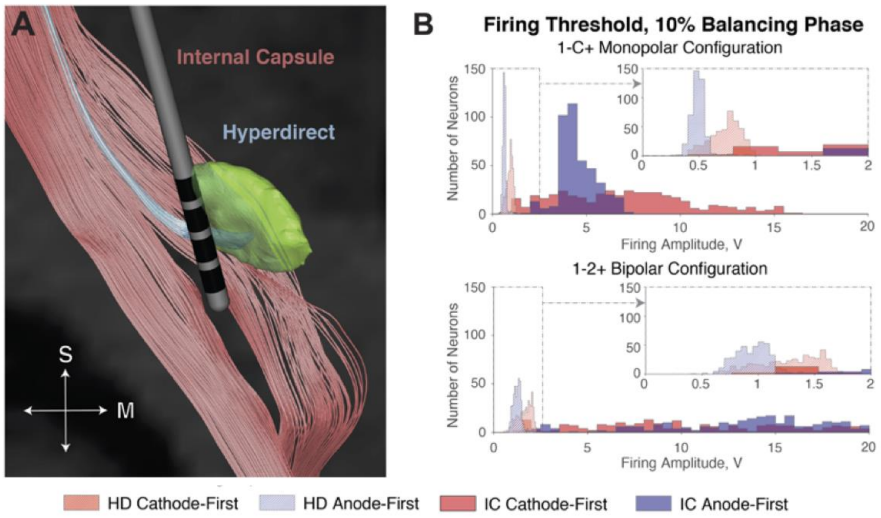


Figure 1. **a.** Visualization of the hyperdirect and internal capsule with respect to the DBS lead. **b.** Firing threshold histograms for hyperdirect and internal capsule tracts given cathodic and anodic stimulation. Anodic stimulation reduces the threshold voltage of orthogonally oriented fibers (hyperdirect), but increases the threshold of passing fibers (internal capsule), which widens the therapeutic window.

Disclosures: G. Duffley: None. **J. Vorwerk:** None. **A.D. Dorval:** None. **C.R. Butson:** F. Consulting Fees (e.g., advisory boards); NeuroPace, Advanced Bionics, Boston Scientific, IntelectMedical, Abbott (St Jude Medical), Functional Neuromodulation.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.04/O9

Topic: C.03. Parkinson’s Disease

Title: Effect of deep brain stimulation (DBS) on spinal cord circuitry in Parkinson's disease

Authors: J. ANDREWS[1], F. ROY[1], *T. SANKAR[2], F. BA[3], R. B. STEIN[4]
[1]Surgery, [2]Neurosurg., [3]Neurol., Univ. of Alberta, Edmonton, AB, Canada; [4]Physiol., Univ. Alberta, Edmonton, AB, Canada

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system affecting up to 10 million people worldwide. Much has been published on changes in cortical motor areas in PD, including the relationship between these changes and the cardinal PD symptoms of bradykinesia, tremor, rigidity, and postural instability. Relatively few studies have focused on pathways within the spinal cord in PD, a key area of output from cortical/supraspinal centers. For the present study, we focused on the effect of descending input from transcranial magnetic stimulation (TMS) on inhibitory reflex circuits within the spinal cord in 9 people with PD being treated with both parkinsonian medication and Deep Brain Stimulation (DBS). We compared these results to 10 age-matched controls. A subthreshold TMS pulse was used to condition a soleus Hoffmann (H)-reflex, an electrically evoked analog of the stretch reflex, to look for potential alterations in reflex mechanisms. Testing was completed under four different treatment conditions 1) OFF treatment (i.e., without medication and DBS turned off); 2) ON medication only; 3) ON DBS only, and 4) ON medication/ON stimulation (i.e., with both treatments active). Motor symptoms in each condition were quantified using Part III of the Unified Parkinson Disease Rating Scale (UPDRS) and correlated with electrophysiological measures. In control subjects, the inhibition of an H-reflex when conditioned by subthreshold TMS delivered 2 ms after peripheral nerve stimulation, was maximal and the H-reflex was reduced to 76 ± 6% of an unconditioned test H-reflex. Note that at this interval, the descending input from TMS would precede the segmental input to the motor neuron pool, thus providing a conditioning effect on the H-reflex. In contrast, in PD OFF treatment, inhibition was reversed, and the H-reflex reached 128 ± 22% of a test response ($P < 0.05$), with the decrease in inhibition correlated with an elevated (i.e., worse) UPDRS-III motor score ($r = 0.68$; $P < 0.05$). When both treatments were ON, inhibition was maximally restored toward control levels (82 ± 11%; $P = 0.67$), and motor symptoms were similarly diminished relative to OFF treatment ($P < 0.05$). The reappearance of inhibition suggests a cumulative effect of both treatments, which tended to be stronger than when medication (90 ± 10%; $P = 0.27$) or DBS (93 ± 13%; $P = 0.29$) were applied separately**.** This research may contribute to improved understanding of changes in spinal cord circuitry that accompany treatment in PD. In particular, these objective neurophysiological measures may help to optimize medication and DBS therapy aimed at countering motor disability in people with PD.

Disclosures: J. Andrews: None. **F. Roy:** A. Employment/Salary (full or part-time):; Alberta Health Services. **T. Sankar:** None. **F. Ba:** None. **R.B. Stein:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.05/O10

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS089470

Title: The subthalamic nucleus is differentially modulated by vocalization and limb movement

Authors: *R. KELLEY[1], K. TJADEN[2], D. M. CORCOS[3], J. D. GREENLEE, M.D.[4]
[1]Univ. of Iowa, Iowa City, IA; [2]Univ. at Buffalo, Buffalo, NY; [3]Dept. of Physical Therapy/Human Movement, Northwestern Univ., Chicago, IL; [4]Dept Neurosurg, Univ. Iowa, Iowa City, IA

Abstract: Deep brain stimulation of the subthalamic nucleus (STN-DBS) exacerbates Parkinson's disease-related vocal motor deficits in select patients. The mechanism behind this is unclear. Few studies have directly compared the role of the STN in vocalization and limb motor activity. To address this question, we recorded neuronal activity form 44 dorsolateral STN single units in 13 intraoperative STN-DBS patients as they performed vocal and limb motor tasks. Patients were instructed to either repeatedly vocalize a syllable (/ɑ/ or /tɑ/) or tap their index finger on the side ipsilateral to an STN recording electrode. Neuronal modulation during vocalization and limb movement was significantly different around both the start ($p = 0.0045$) and end ($p = 0.018$) of performance blocks. Electrode depth and laterality within the dorsolateral STN did not significantly correlate with neuronal modulation. Electrode position along the anterior-posterior axis showed a slight trend towards significance ($p = 0.19$). Differential patterns of neuronal modulation can be detected in intraoperative STN-DBS patients and may help predict susceptibility to STN-DBS-induced vocal motor impairment. These findings aim to address a major complication in STN-DBS for Parkinson's disease.

Disclosures: R. Kelley: None. **K. Tjaden:** None. **D.M. Corcos:** None. **J.D. Greenlee:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.06/O11

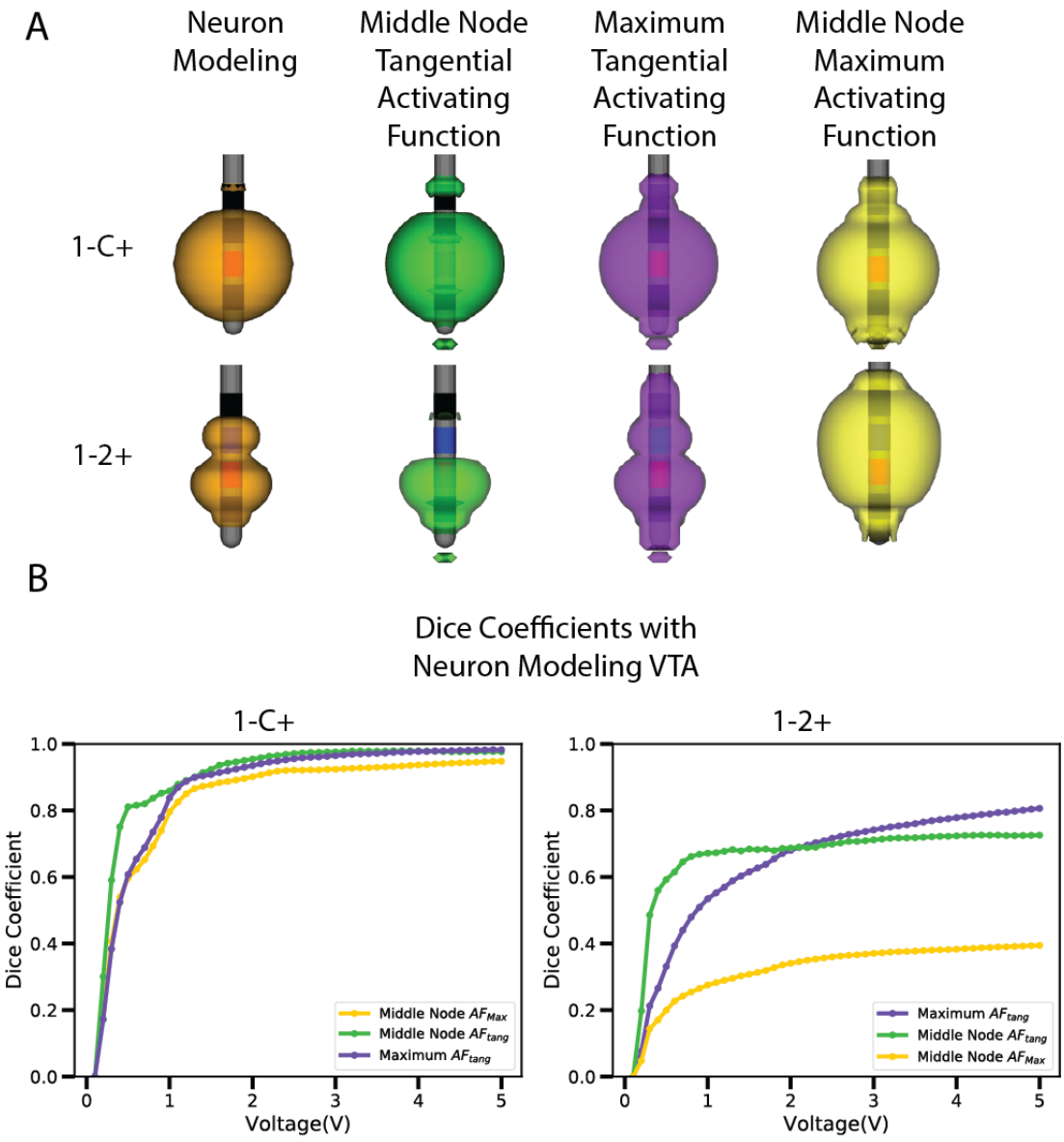
Topic: C.03. Parkinson's Disease

Support: NIH Grant NR014852

Title: The activating function based volume of tissue activated: An axon orientation and projection independent method for predicting neural activation by deep brain stimulation

Authors: *G. DUFFLEY[1], D. N. ANDERSON[2], J. VORWERK[2], A. D. DORVAL[3], C. R. BUTSON[4]
[1]Bioengineering, [3]Dept. of Bioengineering, [4]Scientific Computing & Imaging Inst., [2]Univ. of Utah, Salt Lake City, UT

Abstract: The volume of tissue activated (VTA) is the spread of activation caused by deep brain stimulation. Computational models of the VTA have been used for a variety of clinical and research applications. Classically, the VTA is calculated by determining activation thresholds for a grid of multicompartment axon models tangential to the electrode in response to electric potential derived from bioelectric field models. The activating function, which is the second spatial derivative of extracellular voltage along an axon, is a known predictor of neuronal activation. In this study, we will demonstrate how the matrix of second spatial derivatives of extracellular potential, the Hessian matrix, can be used to calculate the VTA without the orientation and projection bias of the standard method.
We compared the activation volumes from the standard VTA to three activating function based metrics: middle node tangential activating function, maximum tangential activating function, and middle node maximum activating function, as derived from the primary eigenvalue of the Hessian matrix. We used NEURON models to establish the relationship between the activating function and axon activation. We used our calculated threshold values to create volumes of our three metrics for comparison with the standard VTA (Fig 1A).
All three of our methods matched the standard VTA for monopolar stimulation, but only the maximum tangential activating function matched for bipolar. The maximum tangential activating function matches the NEURON models because it considers the off-centered nodes that are the sites of action potential initiation of the NEURON models located near the anodic contact. In bipolar stimulation, the middle node maximum activating function predicts a much larger volume because it considers all orientations of fibers, some of which are much more excitable compared to the tangential fibers used in the standard VTA. The maximum activating function, as derived from the Hessian, better predicts activation because it considers all possible fiber orientations.



A) Surfaces generated by our four methods for the Medtronic 3389 DBS electrode at 3.0V amplitude, 90µs pulse width, and medium impedance. B) The dice coefficients of overlap between the NEURON modeling results and the three Hessian-based metrics. Overall, all monopolar simulation methods have high overlap. With bipolar stimulation, maximum tangential activating function performs best, and maximum activating function predicts a larger volume of activation.

Disclosures: G. Duffley: None. **D.N. Anderson:** None. **J. Vorwerk:** None. **A.D. Dorval:** None. **C.R. Butson:** F. Consulting Fees (e.g., advisory boards); NeuroPace, Advanced Bionics, Boston Scientific, IntelectMedical, Abbott (St Jude Medical), Functional Neuromodulation.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.07/O12

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01NS097782

Title: Hand movement and therapeutic deep brain stimulation differentially modulate cross regional pallidocortical phase amplitude coupling in Parkinson's disease

Authors: *M. MALEKMOHAMMADI[1], N. AUYONG[2], A. O'KEEFFE[2], N. POURATIAN[2]
[1]Los Angeles, CA; [2]UCLA, Los Angeles, CA

Abstract: ***Introduction:*** Multiple lines of evidence suggest that beta band (13-25 Hz) hypersynchrony, including pallidocortical coherence and cortical phase amplitude coupling (PAC), contribute to the pathophysiology of Parkinson disease (PD) and are suppressed by therapy; such as deep brain stimulation (DBS). In our previous work, we have shown that in addition to local cortical PAC, subcortical-cortical PAC (between thalamus and cortex) exists and encodes functional connectivity. In this work, we aimed to explore the pallidocortical PAC to better understand network synchrony. Our working hypothesis is that this hypersynchronized state results in basal ganglia binding and thereby inhibiting normal motor cortical function. ***Methods:*** We recorded local field potentials (LFPs) from pallidum and ipsilateral sensorimotor cortices through a non-penetrating electrocorticography (ECoG) strip in twenty-two subjects with PD undergoing pallidal DBS implantation surgery. Data was recorded during DBS-OFF condition while subjects alternated between a 30-second block of rest and contralateral hand movement (finger tapping). In a subset of nine subjects, similar recordings were obtained during DBS-ON condition. We measured effects of movement and stimulation on interregional beta-broadband gamma (50-200 Hz) PAC. ***Results:*** Pallidocortical beta-broadband gamma PAC was statistically significant across the cohort and is spatially specific to the motor cortex. This coupling was maximal at 22.64±6.74 Hz (high beta) and correlated with symptoms of rigidity and bradykinesia (Rho = 0.68 P= 0.02). Contralateral hand movement and pallidal stimulation significantly suppressed the pallidocortical PAC (P=0.015 and 0.03, respectively). With movement, the frequency of maximal coupling remained unchanged (P=0.1). However, with therapeutic stimulation, the frequency of maximal coupling shifted to the low beta range (18.21±5.38 Hz). While movement related suppression of PAC was correlated with changes in local pallidal beta power (R2 = 0.7, P=0.03), stimulation did not demonstrate this correlation (R2 = 0.03, P=0.6). ***Conclusions:*** Pallidal (phase)- motor cortical (amplitude) PAC in the high beta range reflects the severity of bradykinesia and therapeutic stimulation suppresses this coupling

independently of changes in local pallidal power. These findings provide further evidence of the role of high beta rhythms in exaggerated network level synchrony in PD.

Disclosures: M. Malekmohammadi: None. **N. AuYong:** None. **A. O'Keeffe:** None. **N. Pouratian:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.08/O13

Topic: C.03. Parkinson’s Disease

Support: NIH R44-103714
R01-NS094206
P50-NS098573

Title: Longitudinal relationships between deep brain stimulation electrode impedances and local field potential recordings in the subthalamic nucleus

Authors: *A. KOVACH-BRINDA[1], A. DOYLE[2], L. WILMERDING[3], J. KRIEG[3], M. JOHNSON[3]
[2]Neurosci., [3]Biomed. Engin., [1]Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Physiological features of local field potentials (LFPs) recorded through deep brain stimulation (DBS) leads hold promise for both identifying therapeutic stimulation configurations and driving neural feedback for closed-loop DBS applications. Studies leveraging LFPs in these contexts have performed these measurements intraoperatively, in an acute phase within days of DBS lead implantation, and in a chronic setting after the electrode-tissue interface surrounding the DBS lead has stabilized. In this study, we tracked the longitudinal dynamics of resting-state LFP signals in the subthalamic nucleus (STN) following implantation of an STN-DBS lead in a non-human primate (macaca-mulatta, 17 yo, female). In conjunction with these recordings conducted over a two-week post-implant period, electrochemical impedance spectroscopy measurements were also collected in parallel. Electrode site impedances significantly decreased from a few hours of implantation to 24 hours post-implant (paired, two-sided Wilcoxon signed-rank test, p=0.03, n=6). Despite these impedance changes, there were non-significant changes in the spectral power of beta band LFP oscillatory activity. Between time periods of putative vasogenic edema (e.g. days 1-2) and putative cellular edema (e.g. day 7-9), DBS electrode site impedances significantly increased in magnitude (paired, two-sided Wilcoxon signed-rank test, p=0.03, n=6) . Over this period, beta band oscillation peak spectral power significantly increased (Mann-Whitney U, p=0.04, n=6). These results suggest that the spectral power of beta-band oscillations is relatively weak in the peri-implant stage as compared with the chronic, post-

implant stage in which electrode site impedance magnitude has significantly increased. The results also suggest that while site impedances and LFP spectral power may not correlate, explicitly, electrochemical impedance spectroscopy can be helpful in relating electrode-tissue interface dynamics to interpretation of LFP recordings.

Disclosures: A. Kovach-Brinda: None. **A. Doyle:** None. **L. Wilmerding:** None. **J. Krieg:** None. **M. Johnson:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.09/O14

Topic: C.03. Parkinson’s Disease

Support: NIH R01 NS091236
NIH R37 NS040894

Title: Frequency-specific optogenetic deep brain stimulation of subthalamic nucleus improves parkinsonian motor behaviors

Authors: *C. YU[1], I. R. CASSAR[1], J. SAMBANGI[1], W. M. GRILL[2]
[1]Dept. of Biomed. Engin., [2]Dept. of Biomed. Engineering, Neurobiology, Electrical and Computer Engineering,Neurosurgery, Duke Univ., Durham, NC

Abstract: Deep brain stimulation (DBS) is a well-established therapy for the motor symptoms of advanced Parkinson's disease (PD) and other neurological disorders. The subthalamic nucleus (STN) is a widely used DBS target and has been proven clinically effective. However, the mechanisms underlying the therapeutic effects of STN-DBS for PD remain less understood. Here we used an opsin (Chronos) with ultrafast dynamics that is able to follow high-frequency DBS, expressed under the control of calcium/calmodulin-dependent protein kinase II (CaMKII) promoter packaged into an adeno-associated virus serotype 5 (AAV5) to generate local cell specific expression in the STN in our rat model of PD. We quantified the behavioral effects of optogenetic DBS of the STN on parkinsonian motor symptoms including circling behavior and forelimb adjusting steps. We recorded single unit activity and local field potential to evaluate changes of neural circuit activity during cell specific optical stimulation in the STN of urethane anesthetized rats (1.2g/kg, subcutaneous). We found that optogenetic stimulation of STN local cells at 130Hz reduced pathological circling behavior, in contrast to previous results with the much slower channelrhodopsin-2 opsin. Importantly, optogenetic DBS of STN exhibited a strong dependence on stimulation frequencies; high frequency DBS (75, 100, 130Hz) relieved ipsilateral turning while low frequency (5Hz and 20Hz) DBS was not effective. In addition, optogenetic DBS at 130Hz in the STN corrected the bias for using the unimpaired forepaw in

forelimb stepping, while low frequency (20Hz) DBS was not effective. High frequency (130Hz) optogenetic stimulation transiently increased or decreased the neural activity in the STN, globus pallidus externa (GPe) and substantia nigra pars reticular (SNr), with more neurons activated in STN and more neurons inhibited in SNr. As well, high frequency stimulation disrupted beta band oscillatory activity in the STN. Together, our results indicated that high frequency optogenetic stimulation of STN local cells was more effective than low frequency stimulation at reducing pathological rotational behavior and improving abnormal stepping. High frequency optical stimulation resulted in modulations of neuronal firing patterns in the STN-associated neural circuit.

Disclosures: C. Yu: None. **I.R. Cassar:** None. **J. Sambangi:** None. **W.M. Grill:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.10/O15

Topic: C.03. Parkinson’s Disease

Support: NIH Grant UH3NS095554

Title: Evaluating the robustness of fiber pathway activation with deep brain stimulation directional and multiple-electrode designs

Authors: *A. JANSON[1], D. N. ANDERSON[2], C. R. BUTSON[3]
[1]Scientific Computing and Imaging Inst., Salt Lake City, UT; [3]Scientific Computing & Imaging Inst., [2]Univ. of Utah, Salt Lake City, UT

Abstract: Clinical outcomes for patients with DBS are highly variable and two critical factors underlying this variability are where and how stimulation is applied. Variability in lead placement for the same target across a patient cohort has also been observed along with computational modeling that has demonstrated how minor variations in lead location and the shape of the electric field can lead to drastic variations in the effects of stimulation. The objective of this study was to evaluate the ability of new directional electrode designs and multielectrode configurations to robustly activate target fiber pathways, with computer simulations, in order to gain insights about how DBS targeting can be improved to handle uncertainty. Our hypothesis is that the use of new directional-steering electrodes or multiple electrodes can compensate for the observed variability in lead placement with respect to the intended target and provide more robust control over fiber activation compared to current cylindrical electrode designs. This means an electrode design or configuration is robust if it is able to provide acceptable stimulation from its contacts to maximally activate the target fiber pathway in scenarios where its location with respect to the target may vary. We found no major

differences in the ability to activate the target fiber bundle for any of the single lead geometries as the lead was placed farther away from the target, but that the use of two DBS leads in close proximity was able to maintain a higher percentage of fiber activation. We anticipate this study will create a framework to assess the benefit of new stimulation technologies and how they can be used to compensate for the observed variability in lead locations.

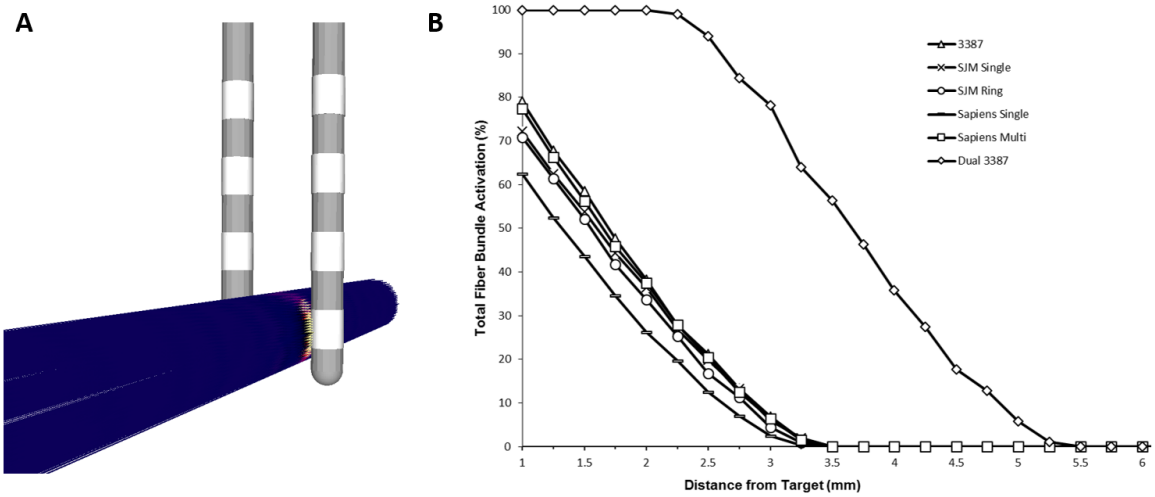


Figure 1. **(A)** Simulation setup with two Medtronic 3387 DBS leads spaced 3.75 mm apart surrounding the target fiber bundle. **(B)** Evaluation of percent fiber bundle activation as lead location distance from target is varied for several DBS lead geometries and the dual lead configuration with amplitude held constant at 1 V.

Disclosures: A. Janson: None. **D.N. Anderson:** None. **C.R. Butson:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.11/O16

Topic: C.03. Parkinson’s Disease

Support: NIH R01 NS090913-01
NIH R25 PAR-13-384

Title: Pallidal deep-brain stimulation disrupts pallidal beta oscillations and coherence with primary motor cortex in Parkinson’s disease

Authors: *D. D. WANG[1], C. DE HEMPTINNE[2], S. MIOCINOVIC[3], P. A. STARR[4]
[1]Neurolog. Surgery, UCSF, San Francisco, CA; [2]Dept. of Neurolog. Surgery, Univ. of California

San Francisco, San Francisco, CA; [3]Neurol., Emory Univ., Atlanta, GA; [4]Neurosurg., Univ. of California San Francisco Dept. of Neurolog. Surgery, San Francisco, CA

Abstract: In Parkinson's disease (PD), subthalamic nucleus beta band oscillations are decreased by therapeutic deep-brain stimulation (DBS) and this has been proposed as important to the mechanism of therapy. The globus pallidus is a common alternative target for PD with similar motor benefits as subthalamic DBS, but effects of pallidal stimulation in PD are not well studied, and effects of pallidal DBS on cortical function in PD are unknown. Here, in 20 PD and 14 isolated dystonia human patients of both genders undergoing pallidal DBS lead implantation, we recorded local field potentials from the globus pallidus and in a subset of these, recorded simultaneous sensorimotor cortex ECoG potentials. PD patients had elevated resting pallidal low beta band (13-20 Hz) power compared with dystonia patients, whereas dystonia patients had elevated resting pallidal theta band (4 - 8 Hz) power compared with PD. We show that this results in disease-specific patterns of interaction between the pallidum and motor cortex: PD patients demonstrated relatively elevated phase coherence with the motor cortex in the beta band and this was reduced by therapeutic pallidal DBS. Dystonia patients had greater theta band phase coherence. Our results support the hypothesis that specific motor phenomenology observed in movement disorders are associated with elevated network oscillations in specific frequency bands, and that DBS in movement disorders acts in general by disrupting elevated synchronization between basal ganglia output and motor cortex.

Disclosures: C. de Hemptinne: None. **S. Miocinovic:** None. **P.A. Starr:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Medtronic. F. Consulting Fees (e.g., advisory boards); Boston Scientific.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.12/P1

Topic: C.03. Parkinson's Disease

Support: MRC UK Grant MC_UU_12024/1
German Research Council SFB 936, Project A2/A3
German Research Council SFB 936, Project C1
German Research Council SFB 936, Project C5
German Research Council SFB 936, Project C8
University of Oxford Clarendon Fund Scholorships
MRC UK MR/M014762/1

Title: Phase-dependent suppression of beta oscillations in Parkinson's disease

Authors: *A. HOLT[1], E. KORMANN[1], A. GULBERTI[2], M. POTTER-NERGER[2], C. MCNAMARA[1], H. CAGNAN[3], S. LITTLE[4], J. KOPPEN[2], C. BUHMANN[2], M. WESTPHAL[2], C. GERLOFF[2], A. K. ENGEL[5], P. BROWN[1], W. HAMEL[2], C. K. MOLL[2], A. SHAROTT[1]
[1]Univ. of Oxford, Oxford, United Kingdom; [2]Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [3]Univ. Col. of London, London, United Kingdom; [4]Sobell Dept. of Motor Neurosci. and Movement Disorders, Inst. of Neurol., London, United Kingdom; [5]Dept. of Neurophysiol. and Pathophysiology, Hamburg, Germany

Abstract: High frequency (≥ 130 Hz) deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for motor symptoms of Parkinson's disease (PD), but is limited by stimulation-induced side effects and partial efficacy. There is a need for an approach which more selectively targets pathological activity while using less electrical current. Exaggerated oscillatory activity in the beta frequency range (12-30 Hz) that can be detected in single basal ganglia neurons and local field potentials (LFPs) has been found to correlate with akinetic/rigid motor symptoms. Importantly, the ability of DBS to reduce pathological beta oscillations is predictive of its effectiveness at reducing these symptoms. We hypothesized that stimulating at a specific phase of the beta oscillation would reduce the amplitude of the oscillation, potentially improving efficacy and efficiency. To test this, low amplitude stimulation (0.5 – 2 mA) near the peak beta frequency was delivered, while recording STN unit activity, LFPs, and EEG simultaneously, in ten patients undergoing surgery for implantation of DBS leads. A novel recording setup, where stimulation was delivered dorsal to the STN, resulting in modulatory effects within the STN as well as the cortex, allowed us to better resolve signals without significant corruption by stimulus artifacts. By analyzing the natural drift in the timing between the stimulation and the ongoing beta oscillation, we demonstrate that for each patient there is a specific phase relationship that, if maintained over multiple cycles (> 2), favors suppression of the local oscillation amplitude, unit beta synchronization and cortico-subthalamic synchronization. After five consecutive pulses at this suppressing phase, the beta amplitude was reduced by 47%, similar to the 50% reduction seen previously using high frequency stimulation (130 Hz). However, in comparison to high frequency stimulation, amplitude suppression was achieved by delivering a stimulus pulse every 50-67 milliseconds instead of every 8 milliseconds and using lower stimulus amplitudes. Unlike phase dependent suppression, amplification was not dependent on the number of consecutive pulses, and resulted in weaker effects (4.7-35.5% amplification). Stimulation pulses led to variable multiphasic responses in STN neurons, suggesting that oscillations were suppressed in the absence of a consistent excitatory or inhibitory effect on spiking. Our findings provide the first evidence for phase dependent suppression of beta oscillations in PD and suggest stimulation timed to the ongoing oscillation could reduce pathophysiological activity with greater selectivity.

Disclosures: A. Holt: None. **E. Kormann:** None. **A. Gulberti:** None. **M. Potter-Nerger:** None. **C. McNamara:** None. **H. Cagnan:** None. **S. Little:** None. **J. Koppen:** None. **C. Buhmann:** None. **M. Westphal:** None. **C. Gerloff:** None. **A.K. Engel:** None. **P. Brown:** None. **W. Hamel:** None. **C.K. Moll:** None. **A. Sharott:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.13/P2

Topic: C.03. Parkinson's Disease

Support: NIH RO1-NS088679
NIH UL1TR000114
NIH R01-NS085188
P41 EB015894
P30 NS076408
MNDrive Fellowship to MP
P50NS098573

Title: Fractional anisotropy within the subthalamic nucleus: An imaging biomarker for early Parkinson's disease? A high-resolution 7Tesla magnetic resonance imaging study

Authors: *R. PATRIAT[1,2], J. KAPLAN[2], J. NIEDERER[2], S. A. HUFFMASTER[3], M. PETRUCCI[3], N. HAREL[2], C. D. MACKINNON[3]
[1]CMRR / Radiology, Univ. of Minnesota, Woodbury, MN; [2]Radiology, [3]Neurol., Univ. of Minnesota, Minneapolis, MN

Abstract: The search for imaging biomarkers of Parkinson's Disease (PD) has predominantly been focused on measures of the substantia nigra (SN), often with mixed or contradictory results. Few studies have investigated the subthalamic nucleus (STN). The STN is a small basal ganglia structure that is difficult to visualize using a common MRI scanner (1.5T or 3T). Most researchers only have access to "one-size-fit-all" templates, which is a particularly inadequate model for small and varying structures, such as the STN. This could explain why no study has reported fractional anisotropy (FA) differences between PD patients and controls within the structure. 7Tesla (7T) MRI enables viewing the boundaries of the STN, thus making possible analysis at the individual level.
In this study, we used high-resolution 7T MRI to study whether characteristics of the STN, such as its volume and FA, can be used as a biomarker for PD. 7T MRI data were acquired for 30 subjects with early PD (age=64±7yr, 13F, disease duration=2.1 ± 2.0yr) and 22 healthy controls (age=55±16yr, 7F). T2 images (400μm in-plane resolution) were used to manually segment the STN of each subject. Further, diffusion images (1.25mm isotropic) were corrected for distortion, motion, and eddy current effects and FA maps were generated. Finally, FA values were averaged over the left and right STN of each subject separately (STN-FA). The STN volumes and FA values were analyzed between groups and post-hoc analyses were performed within the PD group.

No significant differences in the number of male and female participants were found between the two groups (p=0.60) but a significant difference was found in age between the two groups (p=0.02). Across all subjects, the STN volumes were 116 ± 23 mm^3 for the left STN and 117 ± 24 mm^3 for the right STN, which is consistent with those reported in the literature. STN volume was significantly smaller in PD patients compared to controls ($p<0.05$). In PD patients, smaller STN volumes were associated with higher the UPDRS motor scores ($p<=0.05$). An ANOVA analysis, controlling for STN volumes, showed that the PD group had decreased FA values in the left and right STN compared to controls (corrected $p<=0.01$).
This abstract reports novel findings including a correlation between motor symptoms and STN volume as well as a significant decrease in STN-FA bilaterally compared with controls. Taken together, the volume and FA changes suggest that neurodegenerative changes in the structure of the STN can occur early in disease and the extent of the change impacts the expression of motor impairment.

Disclosures: **R. Patriat:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences. F. Consulting Fees (e.g., advisory boards); Cardionomic, Inc.. **J. Kaplan:** None. **J. Niederer:** None. **S.A. Huffmaster:** None. **M. Petrucci:** None. **N. Harel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences. **C.D. MacKinnon:** None.

Poster

654. Parkinson's Disease: Deep Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 654.14/P3

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Parkinson Study Group and the Parkinson's Disease Foundation's Advancing Parkinson's Treatments Innovations Grant
MnDRIVE brain condition fellowship
NSF IGERT DGE-1069104
NIH NS098573-02

Title: Closed-loop algorithm for optimizing deep brain stimulation in parkinson's disease using an objective measure of rigidity

Authors: *K. H. LOUIE[1], M. N. PETRUCCI[2], P. J. TUITE[2], T. I. NETOFF[1], C. D. MACKINNON[2], S. E. COOPER[2]
[1]Biomed. Engin., [2]Neurol., Univ. of Minnesota, Minneapolis, MN

Abstract: Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus (GP) can dramatically improve the cardinal motor signs of Parkinson's disease (PD). Programming of stimulation settings is done through a trial-and-error process that is time-consuming and it is often uncertain if optimal settings have been attained. The process is further impeded by the use of somewhat subjective clinical ratings to assess the severity of motor signs. In this project, we explored the feasibility and efficacy of a closed-loop strategy that used a Bayesian optimization algorithm in combination with an objective measure of rigidity to rapidly converge upon the stimulation frequency that optimally reduces rigidity.
Materials and Methods: Rigidity was measured in five participants with GP (n = 2) or STN (n = 3) stimulators at stimulation frequencies between 10-185 Hz (increments of 5 Hz) while keeping the contact, amplitude, and pulse width at their clinical optimized settings. The participant's forearm was passively moved through pronation and supination for 20s by a robotic manipulandum to quantify rigidity. Data at each tested frequency was used post-hoc in a simulation of the Bayesian optimization algorithm. Feasibility and efficacy of the Bayesian optimization algorithm was evaluated through two comparisons: the number of frequencies to test and the minimum rigidity found.
Results: Preliminary data suggest that the algorithm can converge to a frequency within 12-15 iterations as opposed to 36 iterations (the necessary amount of iterations to explore all frequencies). The Bayesian optimization algorithm converged to the minimum rigidity measured in 4 of the participants. In one participant, the algorithm converged to a rigidity value that was 103% of the minimum rigidity measured.
Conclusions: The data suggest that the time to achieve optimization of one DBS parameter may be reduced by 60% with the Bayesian optimization algorithm. Ultimately, this approach could significantly decrease the amount of time spent optimizing multiple DBS parameters and lead to a more immediate improvement of quality of life for PD patients.

Disclosures: K.H. Louie: None. **M.N. Petrucci:** None. **P.J. Tuite:** None. **T.I. Netoff:** None. **C.D. MacKinnon:** None. **S.E. Cooper:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.01/P4

Topic: C.03. Parkinson's Disease

Support: NIH Grant AG050718
APDA

Title: Effects of dietary amino acids on parkinson's disease-related phenotypes in a LRRK2 *Drosophila* model

Authors: *V. G. CHITTOOR, I. MARTIN
Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Parkinson's Disease (PD) is a neurodegenerative disease which affects locomotor abilities from the loss of dopamine neurons in the brain. Mutations in LRRK2 (leucine-rich repeat kinase 2) are a common cause of familial PD and a subset of sporadic cases. The most common pathogenic G2019S mutation enhances the kinase activity of LRRK2 leading to an increase in bulk protein translation in the brains of *Drosophila melanogaster*. This aberrant protein translation contributes to the age-related loss of dopaminergic neurons and locomotor deficits observed in G2019S LRRK2 transgenic flies. Protein translation is critically regulated by dietary amino acids, through the TORC1 (target of rapamycin complex 1) pathway. To test if mutant LRRK2-associated phenotypes can be modulated through amino acids, transgenic flies were fed throughout adulthood with synthetic diets comprising of different amino acid levels. Here we found that low and high amino acid diets, within a defined range, result in better retention of dopamine neurons and motor function in aged G2019S LRRK2 flies. Concomitantly, there is a reduction in protein translation in mutant LRRK2 flies on these altered diets. Thus, our study shows a clear correlation between dietary amino acids modulation and mutant LRRK2-associated PD-phenotypes, using a fly model.

Disclosures: V.G. Chittoor: None. **I. Martin:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.02/P5

Topic: C.03. Parkinson’s Disease

Title: Neuron-released alpha-synuclein triggers neuro-inflammatory responses via lrkk2 and nuclear translocation of nuclear factor of activated t-cells (nfat1)

Authors: *C. KIM[1], M. IBA[1], K. RAVINDRAN[1], A. KAGANOVICH[1], A. MAMAIS[1], A. ADAME[2], M. KIM[3], R. RISSMAN[2], S. YOU[3], S.-J. LEE[4], M. COOKSON[1], E. MASLIAH[1]
[1]Lab. of Neurogenetics, Natl. Inst. on Aging, Bethesda, MD; [2]Dept. Neurosciences, Sch. of Medicine, Univ. of California, San Diego, La Jolla, CA; [3]Departments of Surgery and Biomed. Sciences, Cedars-Sinai Med. Center, Los Angeles,, Los Angeles, CA; [4]Dept. of Biomed. Sciences, Neurosci. Res. Institute, and Dept. of Medicine, Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Abnormal deposition of a-synuclein and neuroinflammation are key contributors to the pathogenesis of Parkinson’s disease (PD) and other synucleinopathies such as Dementia with Lewy bodies and Multiple system atrophy. In PD and related disorders, α-synuclein aggregates

are released from neurons inducing activation of microglia, a brain resident immune cell through TLR2, thereby increased cytokine production, proliferation, nitric oxide (NO) production, and intracellular reactive oxygen species production (iROS). However the molecular mechanisms as to how extracellular α-synuclein-mediated triggers such pro-inflammatory microglial responses. Here, we show a role of Leucine-rich repeat kinase 2 (LRRK2), a PD-associated gene in the signaling of extracellular α-synuclein-mediated microglial activation. Exposure to extracellular α-synuclein (released from neuronal cells) increased the phosphorylation of LRRK2 and its kinase activity in the mouse primary microglia through TLR2. In contrast, genetic depletion or pharmacological inhibition of LRRK2 selectively reduced extracellular α-synuclein-mediated microglial responses. Among the series of responses, inhibition of LRRK2 only reduced microglial proliferation and expressions of TNFα and IL-6 while other responses, such as expression of IL-1β were not affected by LRRK2 inhibition. We also demonstrated that activation of microglial LRRK2 by extracellular α-synuclein increased nucleus translocation of Nuclear factor of activated T-cells (NFAT1), a selective transcription factor. The level of nucleus NFAT1 was increased in the microglia of PD mouse model, while it was clearly reduced by administration of functional LRRK2 inhibitor. Furthermore, LRRK2 functional inhibition significantly reduced neurotoxicity, deposition of α-synuclein, and some of cytokine expression, such as TNFα and IL-6. Hence, we propose that modulation of LRRK2 and its downstream signaling mediator NFAT1 will be a novel therapeutic strategy for Parkinson's disease and related synucleinopathies.

Disclosures: C. Kim: None. **M. Iba:** None. **K. Ravindran:** None. **A. Kaganovich:** None. **A. Mamais:** None. **A. Adame:** None. **M. Kim:** None. **R. Rissman:** None. **S. You:** None. **S. Lee:** None. **M. Cookson:** None. **E. Masliah:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.03/P6

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation for Parkinson´s Research (USA)
Spanish Ministry of Economy and Competitiveness (SAF2014-58653-R)
Spanish Ministry of Economy and Competitiveness (SAF2017-89402-R)
BBVA Foundation (Spain)

Title: Pathogenic LRRK2 alters endolysosomal trafficking through impairing Rab8a function

Authors: *P. RIVERO-RÍOS[1], J. MADERO-PÉREZ[1], A. P. THOMAS[2], E. GREGGIO[3], S. HILFIKER[1]

[1]IPBLN-CSIC, Granada, Spain; [2]New Jersey Med. Sch. Rutgers, Newark, NJ; [3]Univ. of Padova, Padova, Italy

Abstract: Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common genetic cause of Parkinson´s disease (PD). LRRK2 regulates various intracellular trafficking pathways in a kinase activity-mediated manner, including endolysosomal degradative events as measured by epidermal growth factor receptor (EGFR) trafficking. Recent studies have revealed a subset of Rab proteins involved in secretory and endocytic recycling events as *in vivo* LRRK2 kinase substrates. However, the effects of such phosphorylation events on endolysosomal membrane trafficking remain unknown. Here, we report that expression of wildtype or phosphodeficient, but not phosphomimetic Rab8a variants rescues the LRRK2-mediated effects on endomembrane trafficking. Similarly, upregulation of the Rab11-Rabin8-Rab8a cascade to activate Rab8a reverts these deficits. In contrast, loss of Rab8a mimicks the effects of LRRK2 on endolysosomal trafficking. Pathogenic LRRK2 expression or loss of Rab8a interferes with EGFR degradation by causing its accumulation in a Rab4-positive endocytic compartment. Taken together, these findings provide a mechanism by which pathogenic LRRK2 deregulates endomembrane transport through impairing Rab8a function.

Disclosures: P. Rivero-Ríos: None. **J. Madero-Pérez:** None. **A.P. Thomas:** None. **E. Greggio:** None. **S. Hilfiker:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.04/P7

Topic: C.03. Parkinson’s Disease

Title: The combined use of pathogenic and protective variants as a tool to explore the role of LRRK2 in autophagy and calcium signalling

Authors: *S. AZEGGAGH, D. C. BERWICK, K. P. S. J. MURPHY, S. A. ALLMAN
Sch. of Life, Hlth. and Chem. Sci., The Open Univ., Milton Keynes, United Kingdom

Abstract: Parkinson’s disease (PD) is the second most common neurodegenerative disease worldwide, affecting 3% of individuals of >75 years of age. The disease is relentless and incurable and the need to understand the causes of PD and develop new treatments is overwhelming. The first events in PD aetiology – the deregulated processes that lead to α-synuclein accumulation and neurodegeneration – remain a mystery. Mutations in the *LRRK2* gene encoding the leucine-rich repeat kinase 2 protein (LRRK2), are the most common cause of familial late-onset Parkinson’s disease (PD) and strongly influence the risk of sporadic PD. LRRK2 pathogenic mutations have been linked to a range of biological processes, including

autophagy, lysosomal activity and intracellular calcium signalling, which notably regulates autophagy. The current study investigates the impact of pathogenic and protective LRRK2 variants on autophagy and calcium signalling. The aim is to gain insight into LRRK2's involvement in the mechanism of autophagy and investigate at which step LRRK2 acts. To do so, we are using cells expressing wild-type or mutated LRRK2 protein and pharmacological inhibitors of LRRK2 kinase and GTPase activities, with autophagy induction monitored by quantification of autophagosomes and western blot. We are confident that our study will yield new and important data about the processes impaired by LRRK2 mutations, and the aetiology of late-onset PD.

Disclosures: S. Azeggagh: None. **D.C. Berwick:** None. **K.P.S.J. Murphy:** None. **S.A. Allman:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.05/P8

Topic: C.03. Parkinson's Disease

Support: NIH R01 NS091719
Sanofi
Michael J. Fox Foundation for Parkinson's Research
American Parkinson Disease Association

Title: Mechanism of G2019S LRRK2-induced neurodegeneration *in vivo*: Role of kinase and GTPase enzymatic activities

Authors: *A. TRAN NGUYEN[1], N. LEVINE[1], E. TSIKA[2], D. MOORE[1]
[1]CNS, Van Andel Res. Inst., Grand Rapids, MI; [2]Brain Mind Inst., Swiss Federal Inst. of Technol. (EPFL), Lausanne, Switzerland

Abstract: Mutations in the *leucine-rich repeat kinase 2* (*LRRK2*, OMIM 607060) gene cause late-onset, autosomal dominant Parkinson's disease (PD) and represent the most common cause of familial PD. Genome-wide association studies suggest that common variation at the *LRRK2* genomic locus also contributes to the risk of idiopathic PD. LRRK2 is a large, multi-domain protein and possesses two distinct enzymatic activities, GTPase and kinase. *LRRK2* familial mutations enhance kinase activity or decrease GTPase activity but commonly induce neuronal toxicity in culture via a kinase-dependent mechanism. While increased kinase activity of LRRK2 has been associated with cell death, the contribution of GTPase activity to neuronal toxicity is poorly understood. Recent findings with *bona fide* kinase substrates of LRRK2 (i.e. RAB10) indicate that familial mutations in the GTPase domain can enhance substrate phosphorylation,

suggesting a critical interplay between the GTPase and kinase domains in mediating the pathogenic effects of LRRK2. However, the role of these enzymatic activities in mediating neurodegeneration in rodent LRRK2 models are incompletely understood. In the present study, we have comprehensively dissected the role of kinase and GTPase activities in regulating neurodegeneration induced by human G2019S LRRK2 in the rat brain. Using adenoviral-mediated gene transfer technology to induce expression of full-length human LRRK2 variants in the rat nigrostriatal dopaminergic pathway, we find that expression of G2019S LRRK2 induces the progressive degeneration of nigral dopaminergic neurons. Interestingly, we demonstrate that the neurotoxic effects of G2019S LRRK2 in this model are rescued by the simultaneous introduction of a kinase-inactive mutation (K1906M). Importantly, we also find that introduction of a GTPase-enhancing mutation (R1398L) or a GTP-binding-deficient mutation (T1348N) significantly attenuate neurodegeneration induced by G2019S LRRK2. Our results demonstrate that G2019S LRRK2 induces neurodegeneration via a mechanism that is dependent on kinase activity as well as GTPase activity in this rat model. Collectively, our study provides important insight into the pathophysiological mechanisms underlying familial *LRRK2* mutations and validates inhibition of kinase activity and modulation of GTPase activity as potential therapeutic strategies for attenuating LRRK2-dependent neurodegeneration in PD.

Disclosures: A. Tran Nguyen: None. **N. Levine:** None. **E. Tsika:** None. **D. Moore:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.06/P9

Topic: C.03. Parkinson’s Disease

Title: The Michael J. Fox Foundation's strategy to generate, characterize, and distribute preclinical antibody tools for investigating Rab molecular biology

Authors: *N. POLINSKI[1], T. N. MARTINEZ[1], M.-Y. CHOU[2], D. R. ALESSI[3], P. DAVIES[3], P. LIS[3], M. MUQIT[3], P. TAYLOR[4], C. HABER[5], S. PADMANABHAN[1], M. BAPTISTA[1], K. D. DAVE[1]
[1]Michael J Fox FDTN, New York, NY; [2]Abcam, Burlingame, CA; [3]Univ. of Dundee, Dundee, United Kingdom; [4]BioLegend, Inc, Dedham, MA; [5]PEPperPRINT GmbH, Heidelberg, Germany

Abstract: A field-wide challenge in Parkinson’s disease (PD) research is a general lack of availability for high-quality, reproducible, and readily accessible preclinical research tools. To address these challenges, The Michael J. Fox Foundation for Parkinson’s Research (MJFF) has developed a growing resource of preclinical tools for the PD research and drug development communities that endeavors to provide researchers with easy access to rigorously validated, research-enabling preclinical tools for molecular biology studies. An important aspect of MJFF’s

preclinical tools portfolio are monoclonal antibodies that target PD-relevant proteins. In collaboration with academic experts and in partnership with Abcam and BioLegend, MJFF has sponsored the custom generation and independent validation of several monoclonal antibodies targeting both total and phosphorylated PD-relevant Rab proteins. The Rab superfamily of proteins function generally in membrane trafficking, and a subset of Rab family members have been identified as key phosphorylation substrates of LRRK2 and PINK1 kinase activity. The ability to detect and visualize these proteins under endogenous conditions would provide us with the opportunity to understand the role of Rabs in PD biology and test their utility as PD-relevant biomarkers. Herein we discuss the general MJFF antibody generation strategy and provide characterization data for ongoing custom antibody development projects, as well as antibody pipeline updates and commercial launch timelines for MJFF's cumulative Rab antibody collection. Ultimately, these MJFF-sponsored antibody projects aim to address field-wide challenges in the PD preclinical tools and reagents landscape and to overall accelerate Parkinson's disease research.

Disclosures: N. Polinski: None. **T.N. Martinez:** None. **M. Chou:** None. **D.R. Alessi:** None. **P. Davies:** None. **P. Lis:** None. **M. Muqit:** None. **P. Taylor:** None. **C. Haber:** None. **S. Padmanabhan:** None. **M. Baptista:** None. **K.D. Dave:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.07/P10

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS076054
NIH Grant R01 NS096240
NIH Grant 2T32AG020506-16

Title: LRRK2 phosphorylation of auxilin mediates synaptic defects in dopaminergic neurons from patients with Parkinson's disease

Authors: *M. NGUYEN, D. KRAINC
Neurol., Northwestern Univ., Chicago, IL

Abstract: Recently identified Parkinson's disease (PD) genes involved in synaptic vesicle endocytosis, such as DNAJC6 (auxilin), have further implicated synaptic dysfunction in PD pathogenesis. However, how synaptic dysfuction contributes to the vulnerability of human dopaminergic neurons has not been previously explored. Here, we demonstrate that the commonly mutated, PD-linked leucine-rich repeat kinase 2 (LRRK2) mediates the phosphorylation of auxilin in its clathrin-binding domain at Ser627. Kinase activity-dependent

LRRK2 phosphorylation of auxilin led to differential clathrin binding resulting in disrupted synaptic vesicle endocytosis and decreased synaptic vesicle density in LRRK2 patient-derived dopaminergic neurons. Moreover, impaired synaptic vesicle endocytosis contributed to the accumulation of oxidized dopamine that in turn mediated pathogenic effects such as decreased glucocerebrosidase activity and increased α-synuclein in mutant LRRK2 neurons. Importantly, these pathogenic phenotypes were partially attenuated by restoring auxilin function in mutant LRRK2 dopaminergic neurons. Together, this work suggests that mutant LRRK2 disrupts synaptic vesicle endocytosis leading to altered dopamine metabolism and dopamine-mediated toxic effects in patient-derived dopaminergic neurons. The work from this project expands the range of proteins for therapeutic intervention to those located at the synapse, potentially leading to the development of targeted treatments for patients with Parkinson's disease.

Disclosures: M. Nguyen: None. **D. Krainc:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.08/P11

Topic: C.03. Parkinson's Disease

Support: work is supported by Reta Lila Weston Institute funds

Title: Investigation of the role of LRRK2 in murine macrophage RAW264.7 cells

Authors: I. NAZISH[1], *R. BANDOPADHYAY[2]
[1]Mol. Neurosci., Reta Lila Weston Institute, UCL Inst. of Neurol., London, United Kingdom; [2]Inst. of Neurol., London, United Kingdom

Abstract: Introduction: Pathogenic mutations and polymorphisms in the LRRK2 gene are linked to familial and idiopathic Parkinson's disease (PD) as well as to two inflammatory conditions, leprosy and Crohn's disease. LRRK2 is expressed strongly in microglia and macrophages indicating its potential role in innate immunity, however, how LRRK2 dysfunction causes PD remains ambiguous. LRRK2 protein harbours two critical enzymatic activities, the kinase and the GTPase making it a highly druggable target for potential PD therapies. Herein, we aimed to establish a link between LRRK2 dysfunction and signalling mechanisms in the murine macrophage cell line (RAW264.7) and the pathological processes in PD.
Materials and Methods: Using WT, T1348N-LRRK2 (this mutation prevents GTP binding) and LRRK2-KO RAW264.7 cell lines, we studied LRRK2 phosphorylation dynamics and TNFα release following treatment with LPS (a proinflammatory mediator) and after treatment with four specific LRRK2 kinase inhibitors. LRRK2 phosphorylation at four specific phospho-sites was monitored using standard immunoblotting and secreted TNFα levels were measured using

ELISA. Statistically significant differences were analysed using ANOVA and T-test using Graph-PAD prism.
Results: LRRK2 phosphorylation significantly upregulated at Ser935/Ser955 residues with LPS (100ng/ml) treatment from 2h-24h in RAW264.7 cells. Kinase inhibition decreased baseline LRRK2 phosphorylation at 4h with LPS treatment reversing the effect. TNFα secretion upregulated following LPS stimulation in both WT and GTPase-deficient cells for both 24h and 48h. However, no significant difference in the basal secretion between the cell lines was seen.
Conclusion: LPS most significantly stimulated phosphorylation of LRRK2 in RAW264.7 WT and GTPase-deficient cells at 4h. Specific LRRK2 kinase inhibitors acted to decrease LRRK2 phosphorylation at Ser935 residue which is a readout of LRRK2 kinase activity. Our preliminary data of TNFα release with LPS treatment appeared to be independent of T1348N mutation.

Disclosures: I. Nazish: None. **R. Bandopadhyay:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.09/P12

Topic: C.03. Parkinson’s Disease

Title: Identification of LRRK2 substrates reveal converging mechanism in familial and sporadic Parkinson’s disease

Authors: *P. S. DESHPANDE[1], D. FLINKMAN[1,2], V. SIINO[2], L. LAUREN[1], L. SUN[1], S. IMANISHI[1], Y. HONG[1], L. ELO[1], V. KAASINEN[3], S. PELTONEN[4], P. JAMES[1,2], E. COFFEY[1]
[1]Turku Ctr. for Biotechnology, Åbo Akademi Univer, Turku, Finland; [2]Immunotechnology, Lund Univ., Lund, Sweden; [3]Div. of Clin. Neurosciences, Turku Univ. Hosp. and Univ. of Turku, Turku, Finland; [4]Dept. of Dermatology, Univ. of Turku and Turku Univ. Hosp., Turku, Finland

Abstract: Parkinson’s disease (PD) is the second most common neurodegenerative disorder accompanied by progressive loss of dopaminergic neurons from the substantia nigra. The exact cause of the disease is unknown and currently there is no cure or treatment to stop the disease progression. PD patients remain asymptomatic in pre-clinical phase and lack of biomarkers for early detection poses a major challenge for testing new treatments. PD is mostly sporadic yet, about 10% of patients report first-degree relative with PD. The G2019S substitution in LRRK2 is the most common cause of autosomal dominant PD and it has been associated with sporadic cases as well. The mutation results in toxic gain of function in LRRK2 kinase activity and gives rise to a phenotype that is clinically indistinguishable from sporadic PD. Thus, understanding LRKK2 function is expected to reveal common pathological mechanisms. We established a

phosphoproteomic screen to identify substrates for LRRK2. This screen revealed several regulators of a key cellular process as novel substrates for LRRK2. Inhibition of LRRK2 kinase activity using LRRK2-IN1, GSK2578215A and MLi-2 stimulated this process in neurons as well as in non-neuronal cells, thus identifying a repressive role for LRRK2. To evaluate if LRRK2 regulated this process in PD, we used fibroblasts cells derived from G2019S and sporadic PD patients. We found that compared to healthy individuals, the process was repressed in fibroblasts from both sporadic and G2019S patients and treatment with LRRK2 kinase inhibitor MLi-2 restored activity to normal levels. In summary, our results identify that LRRK2 regulates a key cellular function and provides a unifying mechanism in familial and sporadic PD. Further evaluation of the underlying mechanisms may provide grounds for early diagnosis and potential new drug targets for treatment of PD.

Disclosures: P.S. Deshpande: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application submitted. **D. Flinkman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application submitted. **V. Siino:** None. **L. Lauren:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application submitted. **L. Sun:** None. **S. Imanishi:** None. **Y. Hong:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application submitted. **L. Elo:** None. **V. Kaasinen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application submitted. **S. Peltonen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application submitted. **P. James:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application submitted. **E. Coffey:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application submitted.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.10/P13

Topic: C.03. Parkinson’s Disease

Support: Michael J. Fox Foundation

Title: Role of leucine-rich repeat kinase 2 in Parkinson’s disease levodopa-induced dyskinesia

Authors: *R. MARONGIU[1], L. VELAZQUEZ[1], J. L. JOYCE[1,2], M. G. KAPLITT[1]
[1]Neurolog. Surgery, Weill Cornell Med., New York, NY; [2]Taub Inst., Columbia Univ., New York, NY

Abstract: The gold standard for treatment of Parkinson's disease (PD) motor symptoms is the restoration of dopamine transmission with administration of the dopamine precursor levodopa. However, approximately 80% of patients develop motor complications, levodopa-induced dyskinesia (LID), which constitute a major cause of disability and limit therapeutic efficacy. Evidence from in vitro and in vivo studies suggest that when substantia nigra dopaminergic neurons degenerate, levodopa treatment can cause LID by altering DA metabolism, gene expression, and neuroplasticity within the dorsal striatum. Recent data suggest that Leucine-Rich Repeat Kinase 2 (LRRK2) protein may be important for striatal response to dopaminergic therapy in PD. LRRK2 has been associated with several key regulators of striatal medium spiny neuron (MSN) function that are involved in LID. LRRK2 mutations were shown to increase membrane presentation of dopamine receptor D1 (Drd1) and downstream signaling cascades. Furthermore, overexpression of wild type (wt) LRRK2 has been reported to negatively regulate PKA activity in MSNs in response to Drd1 activation, while LRRK2 knockdown induced a significant increase of PKA levels in striatal dendritic spines. We hypothesize that disruption of LRRK2 levels via either PD-associated G2019S LRRK2 mutation or inhibition of endogenous LRRK2 with short-hairpin RNA (shRNA) interference will promote LID in the unilateral 6-hydroxydopamine (6OHDA) mouse model of PD. To test the influence of G2019S LRRK2 on LID, we 6OHDA lesioned transgenic mice overexpressing either human wt or G2019S LRRK2 and, two months post-surgery, upon quantifying the lesion efficiency, we induced LID by administering a daily levodopa treatment (6 mg/kg). We scored locomotor, axial, limb and orolingual LID for 3 weeks and found that mice overexpressing either wt or G2019S LRRK2 had no difference in development of LID compared with non-transgenic littermates. Secondly, we generated AAV vectors to inhibit mouse LRRK2 (AAV-sh.LRRK2) and control vector (AAV.sh.Luciferase), and injected it unilaterally into the dorsal striatum of 6OHDA lesioned C57Bl/6 mice. Upon induction of LID as reported above, we surprisingly found that inhibition of striatal LRRK2 expression significantly increased LID scores by 40% compared with control mice suggesting that endogenous striatal LRRK2 may be a key regulator of the LID response to dopaminergic pharmacotherapy. Notably, our data raises questions about the potential unintended effects of experimental therapies targeting LRKK2 inhibition on striatal function, and specifically on the response to dopamine replacement therapy in patients with PD.

Disclosures: R. Marongiu: None. **L. Velazquez:** None. **J.L. Joyce:** None. **M.G. Kaplitt:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.11/P14

Topic: C.03. Parkinson's Disease

Support: NIH R01 NS091719
American Parkinson Disease Association

Title: Role of ArfGAP1 phosphorylation and expression in LRRK2 induced neurodegeneration

Authors: *M. ISLAM, D. MOORE
Van Andel Res. Inst., Grand Rapids, MI

Abstract: Mutations in the *leucine-rich repeat kinase 2* (*LRRK2*) gene cause late-onset, autosomal dominant Parkinson`s disease (PD). *LRRK2* encodes a multi-domain protein containing functional GTPase and kinase domains, and familial mutations located within these domains influence enzymatic activity (i.e. R1441C and G2019S). ArfGAP1 was identified as a GTPase-activating protein (GAP)-like protein for LRRK2 that enhances its GTPase activity and ArfGAP1 also serves as a robust substrate of LRRK2-mediated phosphorylation. Importantly, ArfGAP1 is critically required for neuronal toxicity induced by G2019S LRRK2 in primary cultures. We sought to explore the contribution of ArfGAP1 phosphorylation to regulating its function and LRRK2-related neurotoxic pathways. Using ArfGAP1 deletion mutants, we find that the major sites of phosphorylation by LRRK2 are located within residues 252-359 and mass spectrometric analysis of phosphorylated ArfGAP1 identifies three major sites (Ser284, Thr291 and Thr292). Null mutations at all three ArfGAP1 phosphorylation sites (S284A/T291A/T292A) are required to inhibit LRRK2-mediated phosphorylation. ArfGAP1 overexpression robustly induces the vesicular dispersal of the Golgi complex in neural cells and blocking phosphorylation at S284, T291 and T292 in combination markedly attenuates this Golgi phenotype. We further find that ArfGAP1 overexpression in primary cortical neurons robustly inhibits neurite outgrowth, and preventing phosphorylation (S284A/T291A/T292A) reduces the neurotoxic effects of ArfGAP1. Our data suggest that phosphorylation of ArfGAP1 at S284, T291 and T292 is required for Arf1-mediated Golgi dispersal and inhibition of neurite outgrowth. To determine whether ArfGAP1 is required for mutant LRRK2-induced neurodegeneration *in vivo*, we used *Drosophila* with a heterozygous deletion of ArfGAP1 combined with the transgenic expression of human R1441C LRRK2. We find that reducing ArfGAP1 expression improves survival and attenuates motor deficits in the R1441C LRRK2 flies. Our data establish the contribution of ArfGAP1 phosphorylation and expression in mediating LRRK2-induced neuronal damage, and further support ArfGAP1 inhibition as a therapeutic target for attenuating mutant LRRK2.

Funding: NIH R01 NS091719, American Parkinson Disease Association, Van Andel Research Institute

Disclosures: M. Islam: None. **D. Moore:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.12/P15

Topic: C.03. Parkinson’s Disease

Support: Fondation de France AAP2010 Engt 00016819
Fondation de France AAP2014 Engt 2014-0052580
PhD fellowship for N. Cresto Association France Parkinson 2016
NeurATRIS Investissement d'Avenir ANR-11-INBS-0011

Title: Alpha-synuclein and LRRK2 cooperation in mitochondrial dysfunctions in Parkinson’s disease

Authors: *G. LIOT, C. GARDIER, N. CRESTO, M.-C. GAILLARD, N. DUFOUR, A. BEMELMANS, E. BROUILLET
Neurodegenerative Dis. Lab. UMR 9199, CEA MIRCen, Fontenay aux Roses, France

Abstract: Parkinson’s Disease (PD) is the most frequent neurodegenerative disease after Alzheimer’s Disease. It is characterized by the selective loss of dopaminergic (DA) neurons in the substantia nigra *pars compacta* (SNpc) and the formation of Lewy bodies, composed primarily of aggregates of α-synuclein (α-syn). Familial forms of PD are due to the duplication/triplication of the gene encoding α-syn, or to certain point mutations, such as the A53T mutation which can accelerate α-syn aggregation. Another gene, encoding the Leucin-Rich Repeat Kinase 2 (LRRK2), also shows automosal dominant mutations linked to PD. Among these, the G2019S mutation is the most frequent leading to familial forms of PD and these patients cannot be clinically distinguished from idiopathic patients. It has also been suggested that α-syn and LRRK2 act in concert in the pathogenesis of PD, and this hypothesis is supported by the *in vivo* results of our laboratory. Indeed, we demonstrated that the AAV-mediated overexpression of $LRRK2^{G2019S}$ in the SNpc of rats increases the dopaminergic cell death induced by the AAV-mediated overexpression of $\alpha\text{-syn}^{A53T}$. Now, our goal is to determine how these two proteins, α-syn and LRRK2, can potentiate neuronal cell death. We focused on the cellular mechanisms linked to mitochondria, as this organelle has been shown to be implicated in the pathogenesis of PD. Moreover, α-syn and LRRK2 have both been found to induce mitochondrial defects. For this purpose, we use a model of rat primary cortical neurons infected with lentiviral vectors in order to overexpress the wild type or mutant forms of α-syn and

LRRK2. We characterize the effect of co-expressing these two proteins on mitochondrial physiology by different biochemical (ATP and ROS production) and imaging methods (mitochondrial morphology) and on cell viability. Preliminary results support the existence of an interplay between α-syn and LRRK2 in the cellular response to a rotenone-induced mitochondrial toxicity.Our long term objective is to find the main pathways impacted by α-syn and LRRK2 to identify new molecular targets and thereafter develop new therapeutic strategies for the treatment of PD.

Disclosures: G. Liot: None. **C. Gardier:** None. **N. Cresto:** None. **M. Gaillard:** None. **N. Dufour:** None. **A. Bemelmans:** None. **E. Brouillet:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.13/Q1

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01 NS076054

Title: The association of LRRK2 and GBA1 in Parkinson’s disease pathogenesis

Authors: *D. YSSELSTEIN, D. KRAINC
Neurol., Northwestern Univ., Chicago, IL

Abstract: Parkinson’s disease (PD) is a neurodegenerative disorder that affects millions of individuals around the world. Mutations in the genes encoding for leucine rich repeat kinase 2 (LRRK2) and glucocerebrosidase (GCase) are strongly associated with onset of PD. The mechanism through which these mutations lead to dopaminergic cell loss in PD is unclear. Recent genetic studies have identified patients with concurrent mutations in the genes for LRRK2 and GCase that develop PD at an earlier age or onset than of patients with just a single mutation in either LRRK2 or GCase. This observation highlights the possibility that mutations in these genes operate synergistically to cause dysfunction in PD patients. Identification of a convergent pathway associated with GCase and LRRK2 mutations could have important therapeutic implications in PD. Using midbrain dopaminergic neurons differentiated from patient-derived induced pluripotent stem cells (iPSCs) containing the LRRK2 mutations, we examined the effect of different LRRK2 mutations on lysosomal GCase activity. We found that neurons containing LRRK2 G2019S or R1441C mutations display reduced lysosomal GCase activity relative to neurons derived from healthy control patients. To further study this, we used CRISPR to create isogenic controls with corrected LRRK2 sequences. We found that these isogenic controls displayed significantly increased GCase activity relative to the corresponding LRRK2 mutant cells. Lastly, we found that treatment of LRRK2 mutant neurons with LRRK2

kinase inhibitors significantly increased lysosomal GCase activity to levels observed in the isogenic control lines. Altogether, these results highlight a potential convergence of LRRK2 and GCase mutations in PD pathogenesis by identifying a possible role for reduced GCase activity in LRRK2-associated PD pathogenesis. These observations suggest that emerging therapies targeted towards GCase activation could also have therapeutic benefits in LRRK2 patients.

Disclosures: D. Ysselstein: None. **D. Krainc:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.14/Q2

Topic: C.03. Parkinson’s Disease

Support: NIH Grant 1RO1 NS095387

Title: Alpha-synuclein-induced dopaminergic neurodegeneration is attenuated by AAV2-TOM20 overexpression

Authors: *B. R. DE MIRANDA, E. M. ROCHA, S. CASTRO-SCHEIRER, J. T. GREENAMYRE
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Both mitochondrial dysfunction and α-synuclein accumulation are implicated in the pathogenesis of idiopathic Parkinson’s disease (PD), and they share a bidirectional relationship; mitochondrial dysfunction results in post-translational modifications that increase α-synuclein toxicity, and α-synuclein accumulation impairs mitochondrial function. Recently, we observed that posttranslationally modified species of α-synuclein directly bind to mitochondrial protein import machinery at the translocase of the outer membrane (TOM)-20 protein, which prevents its association with co-receptor TOM22, and the import of protein into the mitochondria. *In vivo* overexpression of monomeric α-synuclein within the substantia nigra results in progressive dopaminergic neuron death that mirrors a parkinsonian phenotype in animal models of PD. Based on these findings, we postulated that overexpression of TOM20 within dopaminergic neurons of the substantia nigra would be protective against α-synuclein-induced cell death. To investigate this, we generated three adeno-associated 2 viral vectors (AAV2) for infusion into the adult rat brain; (1) AAV2-α-synuclein (2) AAV2-TOM20 and (3) AAV2-GFP (control vector). Unilateral, stereotactic co-injections of AAV2-α-synuclein/GFP, AAV2-α-synuclein/TOM20 or AAV2-TOM20/GFP (control) were performed on adult (7-9 month), male Lewis rats followed by a 12-week incubation period. Histopathological analysis revealed significant loss of dopaminergic neurons from the substantia nigra in animals receiving the AAV2-α-synuclein/GFP vector, however, this neurodegeneration was attenuated in animals co-expressing

AAV2-α-synuclein/TOM20. Neuroprotection against α-synuclein toxicity correlated with a significant preservation of the protein NDUFS3 (NADH:Ubiquinone Oxidoreductase Core Subunit S3), a core subunit of the mitochondrial electron transport chain (complex I), which is imported through the TOM20 presequence receptor. Importantly, we observed that overexpression of AAV2-TOM20 did not result in decreased total α-synuclein protein expression driven by the AAV2-α-synuclein vector. Together, these data implicate that mitochondrial dysfunction caused by α-synuclein plays a central role in the death of dopaminergic neurons, and selective targeting of mitochondrial protein import may be a novel therapeutic strategy to mitigate neurodegeneration in PD.

Disclosures: B.R. De Miranda: None. **E.M. Rocha:** None. **S. Castro-Scheirer:** None. **J.T. Greenamyre:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.15/Q3

Topic: C.03. Parkinson’s Disease

Support: NIH 1R01 NS095387
NIH 1R01NS100744
American Parkinson Disease Association
Ri.MED Foundation

Title: A central role for lrrk2 in idiopathic Parkinson's disease

Authors: *R. DI MAIO[1], E. K. HOFFMAN[1], E. M. ROCHA[1], M. T. KEENEY[1], L. H. SANDERS[2], B. R. DEMIRANDA[2], A. ZHARIKOV[1], A. VAN LAAR[1], A. STEPAN[3], T. A. LANZ[3], J. K. KOFLER[4], E. A. BURTON[5], D. R. ALESSI[6], T. G. HASTINGS[5], J. T. GREENAMYRE[5]
[1]Neurol., Univ. of Pittsburgh, Pittsburgh, PA; [2]Neurol., Duke Univ., Durham, NC; [3]Pfizer Worldwide Res. and Develop., Cambridge, MA; [4]Pathology, [5]Neurol., Univ. of pittsburgh, Pittsburgh, PA; [6]Univ. of Dundee, Dundee, United Kingdom

Abstract: Parkinson’s disease (PD) is a common neurodegenerative disease that results in motor impairment, cognitive and psychiatric symptoms and autonomic dysfunction. Despite the numerous gene mutations responsible for familial PD, about 90% of cases are “idiopathic” (iPD). Missense mutations in leucine-rich repeat kinase 2 (LRRK2), the most common cause of autosomal dominant PD, account for about 3% of cases overall; however, the role of wildtype LRRK2 in iPD is unclear. There is growing consensus that certain LRRK2 mutations increase autophosphorylation at Ser1292, conferring to the enzyme an aberrantly enhanced kinase activity

strongly implicated in PD pathogenesis.
LRRK2 kinase activity state under various conditions and LRRK2/14-3-3 proteins interaction – a biochemical event that modulates LRRK2 activity – have been generally assessed using proteomic approaches, limiting the anatomical or cellular resolution. This constitutes a critical barrier to understanding the role of LRRK2 in PD. We have developed and validated novel proximity ligation (PL) assays with excellent anatomical resolution that can rapidly provide information regarding activation state, cellular localization and physiological regulators of LRRK2.
Using this and other assays, we provide evidence that LRRK2 kinase activity is aberrantly increased in vulnerable dopamine neurons of individuals with idiopathic PD. We also show that LRRK2 kinase activity (i) can be oxidatively increased by mitochondrial impairment or α-synuclein overexpression, (ii) modulates the phosphorylation levels of the Rab GTPase Rab10, (iii) causes endo-lysosomal dysfunction and (iii) accumulation of phosphorylated α-synuclein. Overall, our work shows that, independent of mutations, wildtype LRRK2 plays a key role in idiopathic PD. LRRK2-directed therapeutics may therefore be useful for most people with PD.
This work was generously supported by 1R01 NS095387, 1R01NS100744, the American Parkinson Disease Association and Ri.MED Foundation.

Disclosures: E.K. Hoffman: None. **E.M. Rocha:** None. **M.T. Keeney:** None. **L.H. Sanders:** None. **B.R. DeMiranda:** None. **A. Zharikov:** None. **A. Van Laar:** None. **A. Stepan:** None. **T.A. Lanz:** None. **J.K. Kofler:** None. **E.A. Burton:** None. **D.R. Alessi:** None. **T.G. Hastings:** None. **J.T. Greenamyre:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.16/Q4

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R15NS096702
NIH Grant P20GM103408
NIH Grant P20GM109095
NSF Grant 0619793
NSF Grant 0923535

Title: VPS35 D620N inhibits autophagy through disrupted hyaluronic acid-CD44 signaling

Authors: *A. A. RAHMAN[1], H. Y. JIN[3], A. SOTO[1], I. STOJKOVSKA[4], J. ALBRIGHT[2], N. LAI[2], P. URQUHART[2], A. WEBB[2], J. VELARDE[2], E. OE[2], C. BROWN[2], B. MORRISON[2]
[1]Biomolecular Sci. Grad. Programs, [2]Dept. of Biol. Sci., Boise State Univ., Boise, ID; [3]Dept. of

Immunol. and Microbial Sci., The Scripps Res. Inst., La Jolla, CA; [4]Northwestern Univ., Evanston, IL

Abstract: The primary clinical motor symptoms of Parkinson's disease (PD) result from loss of dopaminergic (DA) neurons in the substantia nigra with autophagy dysfunction being closely linked to this disease. Autophagy is a cellular process responsible for degradation of organelles, macromolecules, and protein aggregates. In PD, characteristic toxic protein aggregates of primarily alpha-synuclein are believed to be substrates for autophagic removal and clearance by autophagy improves preclinical model outcomes. Therefore, modulation of autophagy may be an effective strategy to combat PD. Recently, a PD-causing mutation in VPS35 (D620N) was reported to block autophagy. However, preliminary investigation by other groups into a causal mechanism was limited to canonical VPS35 protein interactors in a cervical cancer cell line. To overcome these limitations, we performed an unbiased screen using RNA sequencing (RNA seq) to identify key pathways affected in a widely used cellular model of PD. We have identified alterations indicative of perturbed extracellular matrix (ECM)-receptor interaction as well as aberrant AKT signaling, a downstream pathway known to regulate the induction of autophagy. Hyaluronic acid (HA) is the major component of brain ECM and signals via CD44, an ECM receptor identified as a top hit by our RNA Seq screen, to the autophagy regulating AKT-mTOR pathway, making this axis a prime candidate for mediating VPS35 D620N autophagy blockade. Additionally, VPS35's well-established role in the retromer complex suggests that altered trafficking of CD44 by the VPS35 mutant may be responsible for the observed repression of autophagy. Our hypothesis is that VPS35 D620N blocks autophagy through dysregulated hyaluronic acid-CD44 signaling by altered trafficking of CD44. Supporting this hypothesis, we find that HA represses autophagy in dopaminergic cells. Furthermore, we report that VPS35 mutant cells exhibit heightened sensitivity to HA signaling suggesting that this might be the mechanism underlying autophagy dysfunction in these cells.

Disclosures: A.A. Rahman: None. **H.Y. Jin:** None. **A. Soto:** None. **I. Stojkovska:** None. **J. Albright:** None. **N. Lai:** None. **P. Urquhart:** None. **A. Webb:** None. **J. Velarde:** None. **E. Oe:** None. **C. Brown:** None. **B. Morrison:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.17/Q5

Topic: C.03. Parkinson's Disease

Support: NIH Grant 1R01 NS095387
NIH Grant 1R01NS100744-01
American Parkinson Disease Association

Title: Mitochondria and nadph oxidase 2 interplay: Relevance in Parkinson's disease

Authors: *M. T. KEENEY[1], E. HOFFMAN[1], J. MCCOY[1], P. J. PAGANO[2], J. T. GREENAMYRE[1], R. DI MAIO[1]
[1]Pittsburgh Inst. for Neurodegenerative Dis., Univ. of Pittsburgh, Pittsburgh, PA; [2]Dept. of Pharmacol. and Chem. Biol., Univ. of PIttsburgh, Pittsburgh, PA

Abstract: Oxidative stress has been described as a major cause of nigrostriatal degeneration in familial and idiopathic Parkinson's disease (PD). Moreover, NADPH oxidase 2 (NOX2) and the mitochondrial electron transport chain, the major enzymatic sources of reactive oxygen species (ROS) in neural cells, appear intimately related in a redox regulatory pathway recently termed *"ROS-induced ROS production"*. While there is some evidence that NOX2 inhibitors may protect dopaminergic neurons against degeneration, these studies have generally been hampered by lack of highly specific inhibitors and an inability to assess the activation state of NOX2 under experimental or pathological conditions with a cellular level of resolution. We now report testing of a novel and highly specific NOX2 inhibitor, NOX2ds-tat, and development of a new proximity ligation (PL) histological assay to detect NOX2 activation. By utilizing this novel histological PL assay and NOX2ds-tat, for the first time, we characterized the nature of the interplay between NOX2 and mitochondria in PD pathogenesis. Specifically, we found that neuronal NOX2 is hyperactive in idiopathic PD brains and in 2 rat models of the disease, rotenone and AAV2-α-synuclein overexpression. Our findings support the hypothesis that in PD, neuronal mitochondrial dysfunction can elicit NOX2 hyperactivity that, in turn, may cause post-translational modifications and accumulation of α-synuclein. This event can initiate a pathogenic cycle that further affects mitochondrial integrity (via impaired protein import) and contributes to the initiation and progression of the disease. Overall, the data suggest that targeting NOX2 may constitute a therapeutic approach in prevention of PD progression.
This work was generously supported by 1R01 NS095387, 1R01NS100744-01 and the American Parkinson Disease Association.

Disclosures: E. Hoffman: None. **J. McCoy:** None. **P.J. Pagano:** None. **J.T. Greenamyre:** None. **R. Di Maio:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.18/Q6

Topic: C.03. Parkinson's Disease

Support: Parkinson's Foundation PDF-FBS-1632
NIH Grant 1R01 NS095387
NIH Grant 1R01 NS100744

MJFF
Merck Sharp & Dohme

Title: Pharmacological inhibition of LRRK2 prevents rotenone-induced neurodegeneration and endolysosomal dysfunction

Authors: *E. N. ROCHA, B. R. DE MIRANDA, R. DI MAIO, S. CASTRO-SCHEIRER, M. T. KEENEY, J. L. MCCOY, J. T. GREENAMYRE
Neurol., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Missense mutations in leucine-rich repeat kinase 2 (LRRK2) are a leading cause of familial Parkinson's disease (PD). Despite consensus that *LRRK2* mutations confer a toxic gain-of-function that results in increased LRRK2 kinase activity, the role of LRRK2 in PD remains unclear. In addition to individuals who inherit a LRRK2 mutation, our laboratory recently demonstrated that increased LRRK2 kinase activity is detected in nigral dopaminergic neurons of sporadic PD-patients. LRRK2 can localize to vesicular structures including endosomes and autophagosomes. It is thought to play a role in vesicular trafficking and autophagy-lysosomal degradation through phosphorylation of various Ras Analog in Brain (Rab) GTPases. At baseline, LRRK2 is a rather low-abundance protein, and sustained LRRK2 activation likely has pathological consequences. Therefore, we aimed to determine whether inhibition of LRRK2 kinase activity can prevent neuropathological abnormalities using an environmentally relevant rodent model of PD. Daily exposure of rats to the mitochondrial complex I inhibitor rotenone for 10-14 days caused many of the pathological features observed in sporadic PD, including dopaminergic degeneration, accumulation of endogenous α-synuclein, and increased LRRK2 kinase activity. These hallmark deficits correlated with impaired endolysosomal trafficking. Rab5, a known LRRK2 kinase substrate and key regulator of early endosomal trafficking, accumulates in dopaminergic neurons in rats treated with rotenone and LRRK2 kinase activity is significantly increased in the same neurons. This accumulation of Rab5 (and our previous report of pRab10 accumulation) may explain how rotenone causes endolysosomal dysfunction and accumulation of undegraded α-synuclein. We hypothesize that LRRK2 contributes to the pathogenesis of PD by disrupting endolysosomal trafficking through excessive phosphorylation of Rabs, including Rab5. In support of this, a specific brain-penetrant LRRK2 kinase inhibitor not only prevented rotenone-induced neurodegeneration but also prevented accumulation of Rab5 and lysosomal dysfunction. These data suggest that specific LRRK2 kinase inhibitors may have broad applicability and be useful for all PD patients. Acknowledgments: This work was supported by a fellowship from the Parkinson’s Foundation (EMR) and grants from the NIH (1R01 NS095387 and 1R01NS100744) and the Michael J Fox Foundation (JTG).

Disclosures: E.N. Rocha: None. **B.R. De Miranda:** None. **R. Di Maio:** None. **S. Castro-Scheirer:** None. **M.T. Keeney:** None. **J.L. McCoy:** None. **J.T. Greenamyre:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.19/Q7

Topic: C.03. Parkinson's Disease

Support: NIH Grant 1R01 NS095387
NIH Grant 1R01 NS100744
American Parkinsons Disease Association

Title: Sex differences in sensitivity to rotenone reflect male-to-female ratios in human Parkinson's disease incidence

Authors: *J. T. GREENAMYRE, E. M. ROCHA, B. R. DE MIRANDA
Neurol., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The male to female odds ratio for incidence of Parkinson's disease (PD) is about 1.5 - 2, indicating that sex differences likely play a role in the pathogenesis of the disease. Many animal models of PD however, do not include sex as a biological variable, possibly overlooking important etiological factors. In male rats, rotenone, an organic pesticide and prototypical mitochondrial complex I inhibitor, reliably reproduces parkinsonism, including motor behavioral deficits of postural instability, rigidity, and bradykinesia at a dose of 2.8 mg/kg/d (i.p.). In addition, rotenone causes the selective neurodegeneration of dopamine neurons in the substantia nigra (SN) and their terminal projections in the striatum (ST), endogenous wildtype α-synuclein accumulation, microglial activation, and changes in iron metabolism. However, our pilot studies in adult female Lewis rats using the same dose of rotenone (2.8 mg/kg/d) did not yield equivalent motor behavioral changes nor dopamine neuron loss or brain pathology. Therefore, we postulated that female rats may be less vulnerable to rotenone-induced neurodegeneration, thus requiring increased exposure to produce an equivalent parkinsonian phenotype to that seen in male rats. To test this, we generated a dose-response using 2.8 mg/kg/d, 3.2 mg/kg/d, or 3.6 mg/kg/d (once daily i.p. injection) of rotenone in female Lewis rats, with one additional group receiving BID dosing (1.6 mg/kg BID = total 3.2 mg/kg/d) of rotenone. Female rats receiving 3.2 mg/kg, 1.6 mg/kg (BID), and 3.6 mg/kg rotenone had a significant loss of dopamine neurons within the SN as assessed by stereology, accompanied by a loss of tyrosine hydroxylase-positive terminals in the ST. Significant microglial activation within the SN was observed in only the 1.6 mg/kg BID and 3.6 mg/kg groups, compared to a marked activation of microglia in male rats receiving 2.8 mg/kg. In addition, following rotenone-treated female animals displayed disparate expression of markers for iron homeostasis, α-synuclein accumulation, and endolysosomal trafficking dysfunction in comparison to male animals. Taken together, these data indicate that female rats display a higher threshold for rotenone-induced pathogenic processes and

neurodegeneration - an effect that parallels human data of higher PD incidence and prevalence in males. This work was supported by the American Parkinson Disease Association and grants from the NIH (1R01 NS095387 and 1R01 NS100744).

Disclosures: J.T. Greenamyre: None. **E.M. Rocha:** None. **B.R. De Miranda:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.20/Q8

Topic: C.03. Parkinson’s Disease

Support: NIH Grant T32 NS007433
University of Pittsburgh Andrew Mellon Predoctoral Fellowship

Title: Neurodegeneration induced by dysregulation of dopamine sequestration is rescued by restoration of vesicular packaging

Authors: *M. L. BUCHER[1], C. W. BARRETT[2], A. D. MORTIMER[2], C. J. MOON[3], J. T. GREENAMYRE[2], T. G. HASTINGS[3]
[2]Neurol., [3]Neurosci., [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Within dopaminergic (DAergic) neurons, dysregulation of vesicular dopamine (DA) packaging results in increased cytosolic DA, which is susceptible to oxidation and degradation: two processes that generate reactive metabolites and reactive oxygen species. There is significant evidence that deficits in vesicular packaging of DA contribute to the pathogenesis of Parkinson’s disease (Miller et al. 1999, Pifl et al. 2014), and animal models have demonstrated toxic consequences following dysregulation of vesicular DA packaging (Caudle et al. 2007, Chen et al. 2008). We have generated a viral vector (AAV2-shVMAT2) that dysregulates vesicular DA packaging by small-hairpin ribonucleic acid (shRNA) interference of rat vesicular monoamine transporter 2 (VMAT2) expression. Unilateral viral-mediated knock-down of VMAT2 results in increased cytosolic DA, as evidenced by increased DA oxidation (27.5%) and turnover (64.6%) (paired t-test, $n=4$, $p<0.05$). Dysregulation of DA packaging resulted in a 38.7% loss of DAergic neurons in the substantia nigra and a corresponding 29.8% loss of tyrosine hydroxylase (TH) intensity in the terminals (paired t-test, $n=5$, $p<0.05$). These data suggest that dysregulation of DA sequestration is sufficient to induce neurodegeneration. To verify that the neurodegeneration was specific to dysregulation of DA, and not an off-target effect of the AAV2-shVMAT2 itself, we developed a viral vector (AAV2-muVMAT2) that expresses human VMAT2 with silent mutations resulting in VMAT2 transcript resistant to the shRNA-VMAT2. The mutant VMAT2 (muVMAT2) construct was first tested *in vitro* in a DAergic neuronal cell line derived from the midbrain of adult rat. Co-expression of muVMAT2 with the shVMAT2 construct decreased the

endogenous rat VMAT2 mRNA but resulted in exogenous human VMAT2 mRNA and an overall increase in VMAT2 protein expression. After cell culture verification, the AAV2-muVMAT2 virus was made for *in vivo* experiments. When co-injected, reintroduction of VMAT2 by AAV2-muVMAT2 restores VMAT2 protein and prevents neurodegeneration compared to a VMAT2 knock-down control that lost 36.17% of VMAT2 protein in transduced neurons (One-way ANOVA, $p<0.001$) and lost 28.00% of DAergic neurons in the substantia nigra (One-way ANOVA, $p<0.05$). These data confirm that neurodegeneration resulting from AAV2-shVMAT2 is specific to VMAT2 knock-down, and further implicate the necessity of DA sequestration to maintain neuronal health in DAergic neurons.

Disclosures: M.L. Bucher: None. **C.W. Barrett:** None. **A.D. Mortimer:** None. **C.J. Moon:** None. **J.T. Greenamyre:** None. **T.G. Hastings:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.21/Q9

Topic: C.03. Parkinson’s Disease

Support: Blechman Family Foundation
NIH Grant 1R21ES027470
American Brain Foundation
American Parkinson Disease Association

Title: Pharmacogenomic repression of alpha-synuclein with beta2 adrenoreceptor agonist is protective in a new rotenone model of delayed, progressive Parkinson's disease

Authors: *A. D. VAN LAAR[1], M. T. KEENEY[1], A. ZHARIKOV[2], S. MITTAL[3], C. SCHERZER[4], J. T. GREENAMYRE[1]
[1]Neurol., Univ. of Pittsburgh, Pittsburgh, PA; [2]Neurol., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [3]Celegene, Cambridge, MA; [4]Neurol., Brigham and Women's Hosp., Boston, MA

Abstract: Excess alpha-synuclein production is a known etiology for some familial forms of Parkinson’s disease (PD), and alpha-synuclein accumulation is a core pathologic feature of idiopathic PD. These findings suggest a central role of alpha-synuclein in PD pathogenesis and have led to speculation that reduction of alpha-synuclein could alter the disease course for idiopathic PD. Our lab has demonstrated that brief exposure of rats to rotenone (2.8mg/kg daily, i.p.) for only 5 days results in a delayed onset, then slowly progressive parkinsonian behavioral phenotype occurring over a period of months. This temporally remote administration of rotenone also causes a gradual increase in alpha-synuclein levels within dopaminergic (DAergic) nigral

neurons, associated with the formation of insoluble Lewy body-like inclusions at later time points. Rats also exhibit a loss of DAergic neurons and increased markers of neuroinflammation in the substantia nigra. Here we examined the effects of pharmacogenomic alpha-synuclein reduction in our new progressive parkinsonian model. We utilized clenbuterol, a brain penetrant β2-adrenoreceptor agonist and asthma medication that has been shown to reduce transcription of alpha-synuclein, and has been epidemiologically linked to a reduced risk of PD. In this study, we pretreated aged Lewis rats (12 months old) with clenbuterol (5mg/kg) in drinking water for 10 days before, then during and after 5 days of rotenone administration. No further rotenone was administered and rats were monitored over 4 months for the development of a parkinsonian phenotype, which emerged spontaneously around 80 days after rotenone. We found that treatment with clenbuterol β2-agonist prevented the progressive parkinsonism seen in the rotenone treated animals without agonist. Exposure to clenbuterol also prevented rotenone-associated DAergic neuron loss (reduced to baseline levels), and reduced alpha-synuclein burden within DAergic cells by -24% as compared to vehicle treated animals receiving rotenone as seen by immunohistochemistry. Down regulation of alpha-synuclein mRNA expression (-52%) was also detected by qPCR in midbrain of agonist-treated compared to vehicle-treated animals triggered with rotenone. β2-adrenergic receptors are also present on microglia, and we found that microglia activation (indicated by IBA1 + CD68 dual labeling) was markedly reduced by clenbuterol treatment. These findings show that lowered alpha-synuclein protein levels in dopaminergic cells prevent the neuropathological cascade following rotenone exposure, further demonstrating its potential as a pharmacotherapy for PD.

Disclosures: A.D. Van Laar: None. **M.T. Keeney:** None. **A. Zharikov:** None. **S. Mittal:** None. **C. Scherzer:** None. **J.T. Greenamyre:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.22/Q10

Topic: C.03. Parkinson’s Disease

Support: NIH R15NS096702
NIH P20GM103408

Title: Target identification and lead discovery for autophagy factors by lipidomic screening

Authors: *A. D. SOTO, B. MORRISON
Boise State Univ., Boise, ID

Abstract: Parkinson’s disease(PD) is the most common motor disease and the second most common neurodegenerative disease. Key hallmarks of the disease are the loss of dopaminergic

neurons in the substantia nigra and autophagy dysfunction. Autophagy is a cellular process responsible for the degradation of organelles, macromolecules, and, toxic protein aggregates. In the case of PD, toxic alpha-synuclein aggregates build up and are the substrate for autophagic degradation. As a result, modulation of autophagy could prove to be an effective target for the treatment of PD. Significant effort has been focused on the identification and characterization of important protein-signaling pathways to regulate autophagy; as a result, considerable progress has been made on this front. However, to date, there have been no clinical treatments that harness autophagy for therapeutic benefit. Therefore, we seek to identify endogenous small lipid molecules that act as signaling mediators for autophagy. In order to accomplish this goal, we have performed an unbiased lipidomic screen using the intracellular lipid chaperone protein FABP5 as "bait". In this study we propose the validation of identified lipid compounds as autophagy modulators in cell culture. We also propose to investigation the molecular mechanisms of action for identified autophagy-regulating lipids using RNA sequencing and subsequent proteomic validation.

Disclosures: A.D. Soto: None. **B. Morrison:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.23/Q11

Topic: C.03. Parkinson's Disease

Title: p53 inducible gene 3 (PIG3) directly modulates apoptotic responses in human neuronal models of Parkinson's disease *in vitro*

Authors: *J. C. CHAUFTY[1], I. D. MAJUMDAR[1], K. HA[1], V. SWAMINATHAN[1], L. SHANAHAN[1], S. AKELLA[1], J. RANJAN[1], R. ROESSLER[1], M. KIEBISH[1], S. GESTA[1], B. SCHUELE[2], V. K. VISHNUDAS[1], N. R. NARAIN[1], R. SARANGARAJAN[1], P. P. NARAIN[1]
[1]Neurol. Dept, BERG, LLC, Framingham, MA; [2]Parkinson's Inst. and Clin. Ctr., Sunnyvale, CA

Abstract: Mutations in the *LRRK2* gene represent a major genetic risk factor for both sporadic and familial Parkinson's disease (PD). However, the mechanistic link between LRRK2 variants and PD-related neurodegeneration remains unclear. We utilized Berg's proprietary Interrogative Biology® methodology to compare primary fibroblasts (FBs) from PD patients harboring the $LRRK2^{G2019S}$ mutation, idiopathic PD patients, and their matched mutation-negative controls (generous gifts from the PI). This study led to identification of the quinone oxidoreductase, PIG3, mechanistically linking $LRRK2^{G2019S}$ to PD pathology. FBs from LRRK2-PD patients demonstrated elevated steady-state PIG3 protein expression that correlated with upregulated MKK3 activity, p38 MAPK phosphorylation, and accumulation of p53. Human dopaminergic SH-SY5Y cells treated with rotenone and 6-hydroxydopamine (6-OHDA) exhibited an increase

in PIG3 expression that correlated with apoptosis. Forced overexpression of PIG3 also compromised cell viability and elevated intracellular oxidative stress in the SY5Y model. Conversely, conditions that attenuate PIG3 expression significantly reduced rotenone- and 6-OHDA- induced cell death in SH-SY5Y cells. These include: siRNA directed against *PIG3,* and small molecule inhibitors of LRRK2 and p38 MAPK (LRRK2-IN-1 and SB203580 respectively). We have also uncovered a direct interaction between PIG3 and catalase in neurons that may modulate redox homeostasis and apoptosis induction. To further examine the role of PIG3 in human PD models *in vitro*, we have reprogrammed fibroblasts from control- and $LRRK2^{G2019S}$-PD donors to generate patient-specific iPS cells. The resulting iPSCs and iPSC-derived neurons (iPSC/Ns) demonstrate *PIG3* transactivation by 6-OHDA and rotenone, supporting observations from the SY5Y cell line. Consistent with their fibroblast counterparts, steady state PIG3 remains elevated in the $LRRK2^{G2019S}$ iPSCs and iPSC/Ns. Subsequently, we utilized the CRISPR/Cas9-system to delete the *PIG3* locus in these patient-specific iPSCs to better understand the contribution of PIG3 in these models. Relative to their isogenic counterparts, $PIG3^{-/-}$ iPSCs and iPSC/Ns exhibit attenuated molecular apoptotic signatures in response to pro-apoptotic stimuli. Here, we also describe the effects of both genetic and neurotoxin-induced PIG3 modulation on neuronal activity *in vitro* using iSPC/Ns. Taken together, our findings reveal that PIG3 contributes to apoptosis in neuronal models of PD and may advance our understanding of the mechanisms behind $LRRK2^{G2019S}$- mediated hypersensitivity to environmental neurotoxins, and neuronal dysfunction.

Disclosures: J.C. Chaufty: A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **I.D. Majumdar:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **K. Ha:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **V. Swaminathan:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **L. Shanahan:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **S. Akella:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **J. Ranjan:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **R. Roessler:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG,LLC. **M. Kiebish:** A. Employment/Salary (full or part-time):; BERG, LLC. **S. Gesta:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **B.**

Schuele: F. Consulting Fees (e.g., advisory boards); BERG, LLC. **V.K. Vishnudas:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **N.R. Narain:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. Other; Co-founder, President & CEO of BERG, LLC. **R. Sarangarajan:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. Other; Co-founder of BERG, LLC. **P.P. Narain:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.24/Q12

Topic: C.03. Parkinson’s Disease

Title: Altered cellular and metabolomic phenotypes observed in LRRK2^{G2019S} patient-specific iPSC-derived neurons are partially rescued in PIG3-deficient cells

Authors: *R. ROESSLER[1], I. D. MAJUMDAR[1], K. HA[1], A. KITAYEV[1], J. RANJAN[1], C. HILL[1], J. CHAUFTY[1], S. GESTA[1], B. SCHUELE[2], V. K. VISHNUDAS[1], P. P. NARAIN[1], R. SARANGARAJAN[1], M. KIEBISH[1], N. R. NARAIN[1]
[1]Berg LLC, Framingham, MA; [2]Parkinson's Inst. and Clin. Ctr., Sunnyvale, CA

Abstract: Parkinson’s disease (PD) is a neurodegenerative disorder that primarily and most severely affects midbrain dopaminergic neurons. A variety of cellular and molecular events, such as increased reactive oxygen species, increased protein aggregation and altered neurotransmitter production have been associated with the disease and contribute to loss of function over time. In order to evaluate deteriorating function of LRRK2^{G2019S} patient-specific iPSC-derived neurons, we analyzed electrophysiological and metabolomic profiles in terminally differentiated dopaminergic (DA) neurons. Interestingly, PD neurons showed different activity patterns in a multi-electrode array analysis as well as altered neurometabolomic profiles assessed by our LC-MS platform. More specifically, we analyzed neuronal firing rates, burst frequencies and network synchrony in LRRK2^{G2019S} DA neurons versus unaffected control DA neurons. In our neurometabolomic analysis we performed an untargeted profiling in order to achieve maximal metabolite coverage as well as profiling focused on dopamine pathway metabolites. In this context we were able to profile components of phenylalanine, tyrosine and tryptophan

metabolism, as well as the antioxidant glutathione. Using BERG's proprietary Interrogative Biology® platform we identified quinone oxidoreductase, PIG3, as a novel molecular candidate associated with the $LRRK2^{G2019S}$ mutation. In the current study, we set out to assess this potential mechanistic link by interrogating the cellular and metabolomic profiles in CRISPR/Cas9 mediated PIG3-deficient isogenic iPSC pairs. Strikingly, we observed partial reversals of the assessed phenotypes in homozygous PIG3 knockout cells compared to isogenic ($PIG3^{+/+}$) $LRRK2^{G2019S}$ patient-specific iPSC-derived DA neurons. Our preliminary findings support the notion that PIG3 might serve as valuable and novel therapeutic target in PD-specific pathologies.

Disclosures: R. Roessler: A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **I.D. Majumdar:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **K. Ha:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **A. Kitayev:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **J. Ranjan:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **C. Hill:** A. Employment/Salary (full or part-time):; BERG, LLC. **J. Chaufty:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **S. Gesta:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **B. Schuele:** F. Consulting Fees (e.g., advisory boards); BERG, LLC. **V.K. Vishnudas:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **P.P. Narain:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **R. Sarangarajan:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. Other; Co-founder of BERG, LLC. **M. Kiebish:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. **N.R. Narain:** A. Employment/Salary (full or part-time):; BERG, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG, LLC. Other; Co-founder, President & CEO of BERG, LLC.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.25/Q13

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS P50NS098685
NIH/ORIP P51OD011132

Title: Differential ultrastuctural reorganization of thalamo-cortical and cortico-cortical glutamatergic innervation in the primary motor cortex of MPTP-treated parkinsonian non-human primates

Authors: *R. M. VILLALBA[1], J.-F. PARE[1], Y. SMITH[1,2]
[1]Yerkes Resch Ctr. and Udall Ctr. of Excelence For Parkinson's Disease, Emory Un, Atlanta, GA; [2]Dept. of Neurol., Emory Univ. Sch. of Medicine. Dept Neurol., Atlanta, GA

Abstract: The loss of dopaminergic neurons in the substantia nigra results in major functional changes of various component nuclei of the basal ganglia-thalamocortical network in Parkinson's disease (PD). However, little is known about the state of connectivity between the basal ganglia-receiving motor territory of the thalamus and motor cortical regions in parkinsonian condition. In a previous study, we have shown a profound reorganization of thalamo-cortical synaptic inputs (vGluT2-positive) in the primary motor cortex (M1) of parkinsonian monkeys (Villalba et al., 2014). In the present study, we analyzed the overall pattern of synaptic connections of cortico-cortical terminals (vGluT1-positive) in layers II-III and Vb of M1 in control and MPTP-treated parkinsonian monkeys, and compared these results with those previously obtained for the thalamo-cortical inputs. Light microscopy analysis has shown an extensive vGluT1 immunostaining in M1 without major differences between layer II-III and Vb in both control and parkinsonian animals. Quantitative ultrastructural results indicate that vGluT1-positive terminals form asymmetric synapses mainly with dendritic spines (55%-65%) in layers II-III and Vb of control and parkinsonian monkeys. The analysis of the post-synaptic densities (PSDs) at both axo-dendritic and axo-spinous synapses revealed a slight increase (less than 10% in layer II-III and layer V) in the percentage of macular synapses in parkinsonian animals. A similar analysis for vGluT2-positive terminals in M1 of parkinsonian monkeys has shown a drastic reduction of thalamo-cortical innervation of layer Vb, and a differential ultrastructural reorganization of thalamo-cortical synapses between layer II-III and Vb. In layer II-III, the proportion of axo-spinous synapses increased from 55% in control animals to almost 70% in parkinsonian monkeys, while in layer Vb, axo-spinous synapses decreased from 90% to almost 70% in the parkinsonian state. Both macular and perforated axo-spinous synapses decreased by 10-12% in layer II-III, and by 5% (macular) and 10% (perforated) in layer Vb in parkinsonian animals,

while macular and perforated axo-dendritic synapses increased by ~10% in layer II-III. However, in layer Vb, the proportion of macular axo-dendritic synapses increased by 15%, while perforated axo-dendritic synapses decreased by ~5% in parkinsonian monkeys. These results help us better understand neuroplastic changes in the microcircuitry of thalamo-cortical and cortico-cortical glutamatergic connections, and increase our knowledge of the cortical pathophysiology in the state of parkinsonism.

Disclosures: R.M. Villalba: None. **J. Pare:** None. **Y. Smith:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.26/Q14

Topic: C.03. Parkinson’s Disease

Support: NIH/NINDS Grant P50-NS098685
NIH/NINDS Grant R01-NS083386
NIH/ORIP Grant P51-OD011132

Title: Ultrastructural features of single pallidothalamic terminals in control and MPTP-treated Parkinsonian monkeys visualized using 3D electron microscopic reconstruction approaches

Authors: *A. J. SWAIN[1,2], H. KELLY[1,2], Y. SMITH[1,2,3]
[1]Yerkes Natl. Primate Res. Ctr., Atlanta, GA; [2]Udall Ctr. of Excellence for Parkinson's Dis. Res., Emory Univ., Atlanta, GA; [3]Dept. of Neurol., Sch. of Med., Atlanta, GA

Abstract: In primates, the internal globus pallidus (GPi) is a main source of basal ganglia GABAergic afferents to the ventral motor thalamus. Functional models of the basal ganglia-thalamocortical circuitry predict that the loss of nigrostriatal dopamine results in an increased GABAergic pallidal outflow to the thalamus in Parkinson’s disease (PD). However, our understanding of the pathophysiology of this increased pallidothalamic activity remains limited. Electrophysiological studies have reported complex changes in firing rates, firing patterns, and oscillatory firing properties of thalamocortical neurons in animal models of parkinsonism and in PD patients. In the striatum and subthalamic nucleus, altered neuronal activity generated in the state of parkinsonism is associated with pre- and post-synaptic structural changes of GABAergic and glutamatergic synapses. The GPi gives rise to large GABAergic terminals that form multiple synapses with single dendrites in the ventral motor thalamus. Based on functional data gathered from structurally-similar terminals in other brain regions, it has been shown that the multi-synaptic morphology of GPi-like terminals creates favorable conditions for inter-synaptic spillover of GABA among the multiple synapses of single terminals. This, in turn, may enable tonic inhibition, even under conditions of high presynaptic firing rates, as is the case in the

parkinsonian state. Thus, an understanding of the plasticity of the ultrastructural features of individual pallidothalamic terminals, such as the number and size of synapses, and volume of terminals, will aid in understanding the impact of altered GPi outflow onto thalamocortical neurons in the state of parkinsonism. To address this issue, we used a Single Block Facing/Scanning Electron Microscopy (SBF/SEM) high resolution 3D electron microscopic approach to quantitatively analyze the morphometry of single GPi terminals in the motor thalamus of control and MPTP-treated parkinsonian monkeys. Preliminary results suggest that the following structural changes take place in parkinsonian animals: 1) the volume of the pallidothalamic terminals is enlarged, 2) the average number of synapses per GPi terminal is decreased, and 3) the flat and surface areas of synapses formed by GPi terminals are increased. These findings suggest that pallidothalamic terminals are endowed with a high level of structural plasticity that may contribute to their increased tonic regulation of thalamocortical outflow in PD.

Disclosures: A.J. Swain: None. **H. Kelly:** None. **Y. Smith:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.27/R1

Topic: C.03. Parkinson’s Disease

Support: P50 NS098685/NS/NINDS NIH HHS/United States
P51 OD011132/OD/NIH HHS/United States

Title: Metabotropic glutamate receptor 5 (mglur5) in the monkey motor thalamus: Subsynaptic association with corticothalamic and cerebellothalamic glutamatergic afferents

Authors: *G. M. JEYARAJ[1], J.-F. PARE[1], Y. SMITH[1,2]
[1]Yerkes Natl. Primate Res. Center, UDALL Cen, Atlanta, GA; [2]Dept. of Neurology, Emory Univ., Atlanta, GA

Abstract: Metabotropic glutamate receptors (mGluRs) are widely distributed throughout the basal ganglia-thalamocortical system, and have been recognized as potential therapeutic targets for Parkinson’s disease. Our understanding of the role and subsynaptic localization of thalamic mGluRs remains limited. Because of its therapeutic relevance, the localization and function of mGluR5 in the basal ganglia has generated significant interest over the past decade. To better understand the potential regulatory role of mGluR5 upon the basal ganglia-related thalamic regions, a deeper understanding of the localization of mGluR5 in the primate motor thalamus is needed. To address this issue, we undertook a detailed electron microscopic analysis of the cellular, subcellular and subsynaptic localization of mGluR5 in the basal ganglia-receiving

regions of the ventral anterior/ventral lateral (VA/VL) and centromedian (CM) nuclei of adult rhesus monkeys, and compared these findings with those gathered from the cerebellar-receiving region of VA/VL. At the light microscopic level, both regions of VA/VL and the CM displayed strong neuropil staining in which laid some mGluR5-positive cell bodies. At the electron microscopic level, mGluR5 immunoreactivity was primarily expressed postsynaptically in dendrites of projection neurons and interneurons (recognized by their content in synaptic vesicles) in the three thalamic nuclei. Occasional immunoreactivity was also encountered in glial processes and putative axonal profiles. Pre-embedding immunogold labeling in VA-VL and CM dendritic profiles of projection neurons and interneurons revealed that 80-85% of gold particles were bound to the extrasynaptic domain of the plasma membrane, whereas 15-20% was intracellular. From the pool of plasma membrane-bound gold particles, a large proportion was found at the edges of the post-synaptic densities of asymmetric synapses formed by putative corticothalamic and cerebellothalamic terminals. The sources of the pre-synaptic boutons was confirmed in double-immunostained tissue for mGluR5 and either vesicular glutamate transporter type 1 (VGluT1-specific marker of cortical terminals) or vesicular glutamate transporter type 2 (VGluT2-specific marker of cerebellar terminals). These findings highlight the widespread expression of mGluR5 in projection neurons and interneurons of the motor thalamus, and provide a solid foundation for the mGluR5-mediated modulation of cortical and cerebellar glutamatergic synapses in the primate motor thalamus.

Disclosures: J. Pare: None. **Y. Smith:** None.

Poster

655. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 655.28/R2

Topic: C.03. Parkinson’s Disease

Support: NIH/NINDS grant P50-NS098685 (Udall Center grant)

Title: Altered excitatory input to GABAergic interneurons in the ventral motor thalamus of MPTP-treated parkinsonian nonhuman primates

Authors: *J.-F. PARE[1], D. ALBAUGH[2], T. WICHMANN[3], Y. SMITH[4]
[2]Yerkes Natl. Primate Res. Ctr., [1]Emory Univ., Atlanta, GA; [3]Dept Neurol, Emory Univ. Sch. Med., Atlanta, GA; [4]Yerkes Natl. Primate Res. Ctr., Udall Ctr. Excel. For Parkinson's Dis. and Dept. of Neurol., Atlanta, GA

Abstract: GABAergic interneurons comprise nearly one third of all neurons in the primate motor thalamus, while they are almost non-existent in the rodent motor thalamus. Despite their abundance in primates, little is known about their synaptic connectivity and functional role in

thalamic processing. Defining the source(s) of their afferent inputs is a prerequisite to a deeper understanding of the mechanisms through which they integrate and regulate the thalamic microcircuitry. Although there is evidence for dysregulation of motor thalamic activity in MPTP-treated parkinsonian monkeys and Parkinson's disease patients, the substrate of these changes remains poorly understood. One potential source of pathological activity changes in the parkinsonian motor thalamus may be altered excitatory inputs to this region. Indeed, unpublished data from our group suggests that the total number of small terminals forming asymmetric synapses (likely corticothalamic terminals) is reduced in the motor thalamus of MPTP-treated parkinsonian monkeys, yet such terminals also tend to form complex multisynaptic contacts onto both thalamocortical and interneuron dendrites in the motor thalamus of parkinsonian monkeys, but not healthy controls. Taken together, these data hint that there may be a selective enhancement of cortical inputs to GABAergic interneurons in the parkinsonian state. To more directly address this question, we have now used electron microscopy to quantify the proportions of asymmetric synapses formed by VGLUT1-positive (ie of cortical origin) terminals onto GABA-labeled dendrites in the motor thalamus of healthy and MPTP-treated parkinsonian monkeys. We analyzed tissue of three healthy and three MPTP-treated monkeys, focusing separately on the basal ganglia- and cerebellar-receiving motor thalamic territories. Remarkably, in both territories, the proportions of asymmetric synapses that involved VGLUT1+ terminals in contact with GABA+ dendrites was markedly enhanced (nearly doubled), further suggesting enhanced corticothalamic innervation of interneurons in the parkinsonian state. For comparison, we also examined, in the same monkeys, the proportion of asymmetric synapses established by vGluT2-positive (ie of cerebellar origin) terminals on GABA+ dendrites in the cerebellar-receiving motor thalamic territory, and did not find obvious differences between healthy and parkinsonian animals. Collectively, these findings strengthen our hypothesis that cortical inputs to motor thalamic GABAergic interneurons are remodeled in the parkinsonian state, which may contribute to the dysregulated activity patterns observed in this region.

Disclosures: J. Pare: None. **D. Albaugh:** None. **T. Wichmann:** None. **Y. Smith:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.01/R3

Topic: C.03. Parkinson's Disease

Support: Canadian Institute for Health Research

Title: Does drug-induced dyskinesia affect voluntary movements of patients with Parkinson's disease?

Authors: *C. DUVAL[1], E. GOUBAULT[2], K. LEBEL[3], S. BOGARD[4]
[1]UQAM, Montreal, QC, Canada; [2]Sci. of Physical Activity, Univ. of Quebec at Montreal, Montreal, QC, Canada; [3]Médecine dentaire, Uniersité de Montréal, Montréal, QC, Canada; [4]Sci. of Physical Activity, Univ. of Quebec At Montreal, Montreal, QC, Canada

Abstract: Introduction. Managing dyskinesia associated with Parkinson's disease (PD) is mainly achieved through medical regimen adjustments, sometimes leading to an increase in PD cardinal symptoms. In that case, it is important to objectively determine i) which cardinal symptom(s) is already present in a patient with PD having dyskinesia, ii) which symptom(s) is problematic in performing activities of daily living (ADL), and iii) which symptom(s) will have an influence on patients' daily tasks and quality of life (QoL). **Methods.** Patients with PD known to experience dyskinesia were recruited for this study. They were equipped with a suit containing 17 inertial sensors that recorded movements during the performance of ADL. The levels of dyskinesia, tremor, bradykinesia and freezing were objectively measured by the sensors. Levels of postural stability and muscle rigidity were assessed by clinical evaluations. Cognitive decline and depression symptoms were calculated by questionnaires MMSE and GDS-15, respectively. Patient's engagement level in daily tasks and the number of activities affected were assessed by the Activity Card Sort test (ACS). The SF12 was used to assess QoL. The threshold for symptomatology detection and abnormal ADL performance were set using data from an age-, gender-matched control group comprised of 69 participants. Logistic regression was used to identify symptoms affecting ADL performance, while ROC curves and Youden indices identified the critical moment (symptomatology level) where performance decreased. The engagement level and QoL of patients experiencing dyskinesia were compared to control participants and non-dyskinetic patients. Then, Spearman correlations and multiple regressions were performed to understand their relationship. **Results.** In a first study with 89 patients, some of those exhibiting dyskinesia also had rest, postural and kinetic tremor (12,7%, 37,1%, et 15,9% respectively), bradykinesia (28,6%), rigidity (55,6%), postural instability (71,4%) and freezing (9,5%). In a second study with 121 patients with PD (some of them participated in the first study), multivariate analysis showed that dyskinesia was not associated with lower performance in ADL, nor with the level of engagement in daily tasks or QoL. In fact, it is the cardinal symptoms of PD such as tremor, postural instability, bradykinesia, rigidity, depression or cognitive symptoms that had negative impacts. **Conclusion.** These results show that PD symptoms can be concomitantly present with dyskinesia, that they are more problematic for ADL performance, and have a greater influence than dyskinesia on QoL or on the participation in daily tasks .

Disclosures: C. Duval: None. **E. Goubault:** None. **K. Lebel:** None. **S. Bogard:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.02/R4

Topic: C.03. Parkinson's Disease

Support: R44- OD024615
R43-OD020186
R21-MH103718
Branfman Family Foundation Grant

Title: Development of high affinity D_2 receptor agonists as PET imaging agents for Parkinson's and schizophrenia: Preclinical studies

Authors: *S. SUBBURAJU[1], A. W. SROMEK[2], P. SEEMAN[4], J. L. NEUMEYER[3]
[1]Program in structural and Mol. Neurosci., McLean Hosp., Belmont, MA; [3]Medicinal Chem. Program, [2]McLean Hospital/Harvard Med. Sch., Belmont, MA; [4]Pharmacol. and Psychiatry, Univ. of Toronto, Toronto, ON, Canada

Abstract: The D_2^{high} receptor is thought to be the functional form of the D_2 receptor to which endogenous dopamine (DA) binds. Elevation of D2high receptors has been demonstrated in various neurological disorders in which the dopaminergic system is affected. In Parkinson's disease (PD), the loss of dopaminergic neurons causes a shift of remaining D_2 receptors into the high affinity state. Evidence for this is supported by the fact that medications used to treat PD have been shown specifically to target the D_2^{high} receptor. In schizophrenia, a higher proportion of D_2 receptors are in the high-affinity state, evidenced by the fact that schizophrenic patients are behaviorally supersensitive to dopamine agonists.
We recently reported the synthesis and receptor binding for D_1^{high}, D_{1low}, D_2^{high},D_{2low}, and D_3^{high} receptors of a series of fluorinated aporphines, and identified two highly promising high affinity D_2^{high} ligands as potential tritiated radioligands for applications in in vitro receptor binding assays and autoradiography studies, MCL-524 and MCL-536. These agonists exhibited no affinity or low affinity for other receptors tested, including serotonin, alpha and beta-adrenergic, benzodiazepine, GABAA, muscarinic, sigma, kappa, and mu opioid receptors, as well as dopamine, serotonin, and norepinephrine transporters and translocator protein.
We evaluated the radioligands [^{3}H] MCL-524 and [^{3}H] MCL-536 in saturation binding studies and competition binding studies using human D_{2long} expressed in CHO cells. In a competition binding assay with the agonist R-(-)-N-n-propylnorapomorphine (NPA) as the competing ligand, NPA had a K_i binding affinity of 0.16 nM. When [^{3}H] MCL-524 was used, NPA was found to have a Ki value of 0.9 nM. Co-incubation with guanylylimidodiphosphate abolished binding to D_2^{high}. We evaluated radioligands [^{3}H] MCL-524 and [^{3}H] MCL-536 for biodistribution in brain

and peripheral tissues in rats. Peak radioactivity levels were detected in the striatum vs. cerebellum between 15-30 minutes post-administration.
In summary, the radioligands [^{3}H] MCL-524 and [^{3}H] MCL-536 display high binding affinity to human D_{2long} and have proven to be superior radioligands for in vitro evaluation in receptor binding assays. Biodistribution studies indicate both radioligands have rapid uptake and selectivity for the striatum. This unique profile makes radiolabeled MCL-536 a versatile tool for diagnostics and therapeutics, and may quantify D_2^{high} sites in schizophrenia and Parkinsonian patients in vivo.

Disclosures: A.W. Sromek: None. **P. Seeman:** None. **J.L. Neumeyer:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.03/R5

Topic: C.03. Parkinson’s Disease

Title: Clinical trial to evaluate the feasibility and neuroprotective potential of photobiomodulation therapy on Parkinson's disease

Authors: *C. MORO[1], J. MOLET[1], D. AGAY[1], N. TORRES[1], S. CHABARDES[1], C. CHABROL[1], S. RENAULT[1], A. POIZAT[1], O. FAIVRE[1], J. MITROFANIS[2], A.-L. BENABID[1]
[1]Cea-Grenoble, Leti-Clinatec, Grenoble, France; [2]Univ. Sydney, Sydney, Australia

Abstract: Parkinson’s disease (PD) is a degenerative disorder that affects movement, due to the progressive death of dopaminergic cells in the midbrain substantia nigra pars compacta of the basal ganglia. Unfortunately, the progression of this cell death has proved difficult to slow and impossible to reverse. The “gold standard” treatments for most patients with PD (dopamine replacement drugs with or without surgery) are effective at attenuating the motor signs, at least initially, but they do not reliably slow the progression of the disease. Thus, there is a large need for new therapeutic strategies for treatment, particularly those that offer neuroprotection against PD insults. Photobiomodulation (λ=600-1070nm) has also been reported to be effective in several diseases, and some studies showed that photobiomodulation therapy improves locomotor activity associated with a neuroprotective effect as determined by rescue dopaminergic cells in mouse and non-human primates models of PD. These data confirm a real potential for the development of light therapy as a novel neuroprotective strategy. To this aim, we developed and qualified and intracranial implantable device delivering near infra-red light into the brain. This device and intracranial photobiomodulation therapy will be evaluated for their feasibility and safety on a clinical trial, and neuroprotective potential of this innovative technic will be also assessed on parkinsonian patients.

Disclosures: J. Molet: None. **D. Agay:** None. **N. Torres:** None. **S. Chabardes:** None. **C. Chabrol:** None. **S. Renault:** None. **A. Poizat:** None. **O. Faivre:** None. **J. Mitrofanis:** None. **A. Benabid:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.04/R6

Topic: C.03. Parkinson's Disease

Support: JSPS grant (Kakenh) JP16717091
AMED grant JP15652696
AMED grant JP15652958

Title: SMA facilitation using fNIRS-mediated Neurofeedback for gait impairment in Parkinson's disease patients: Interim analysis of randomized clinical trial

Authors: *M. MIHARA[1,2,4], H. OTOMUNE[2,5], Y. KAJIIYAMA[2], H. FUJIMOTO[5], Y. MITANI[1,2], N. HATTORI[4,2], Y. WATANABE[3], Y. SUNADA[1], H. MOCHIZUKI[2]
[1]Dept. of Neurol., Kawasaki Med. Sch., OKAYAMA, Japan; [2]Dept. of Neurol., [3]Dept. of Radiology, Osaka Univ. Grad. Sch. of Med., Suita, Japan; [4]Div. of Clin. Neuroengineering, Osaka Univ. Global Ctr. for Med. Engin. and Informatics, Suita, Japan; [5]Neurorehabilitation Res. Inst., Morinomiya Hosp., Osaka, Japan

Abstract: Background:
Gait impairment including the freezing of gait (FOG) is the one of distinctive features of the patients with Parkinson's disease (PD) and has detrimental effect on their activities of daily living (ADL). Previous studies suggested the cortical and cortico-subcortical network dysfunction may contribute gait disturbance in PD patients including FOG. Among various cortical areas, the dorsomedial portion of motor cortex including the supplementary motor area (SMA) is suggested to play an important role in balance and gait control in human. Based on these findings, we hypothesized that SMA facilitation using functional near infrared spectroscopy mediated neurofeedback system (fNIRS-NFB) might help to improve gait impairment in PD patinets.
Objective:
To investigate the safety and efficacy of the fNIRS-NFB targeting the SMA activity combined with mental practice for the gait disturbance in PD patients through a randomized clinical trial. In this RCT, we are planning to include 40 PD patients with gait disturbance. To exclude the possible detrimental effect of the sham neurofeedback or fNIRS-NFB itself, we performed the interim analysis.
Methods:

Clinically established PD patients (N = 17, 7 males, Age : 75.0 ± 5.0, 6.2 ± 4.6 years from clinical onset) with written informed consent have participated. In addition to the usual inpatient rehabilitation up to 80min/day for two weeks, they participated 6 sessions of mental practice with motor imagery of gait and postural related task concurrent with neurofeedback of the SMA activation. Clinical measures including MDS-UPDRS, Hoehn-Yahr stage, and mini-mental state examination (MMSE), are assessed as baseline characteristics. Gait and balance measures including Timed Up-and-go test (TUG), Freezing of gait questionnaire (FOGQ), Berg Balance Scale (BBS), and Gait speed are also assessed before and after 2 weeks of intervention. Subjects are randomly assigned to 2 groups (REAL and SHAM). Neither patients nor physicians did not recognize which group they were assigned (double blinded).
Results:
Baseline clinical characteristics were comparable between two groups. There was non-significant trend for interaction between group and TUG time with more improvement in the REAL group (time×group interaction :$F_{2,14}$=2.58, p=0.096. TUG gain: t_{15}= 1.89, p=0.086). SHAM group did not show any detrimental effect on TUG (95%CI for immediate effect: -24.7sec to 7.9 sec, t_7=-1.22, p=0.26), and here was no adverse effect associated with fNIRS-NFB in both groups.
Conclusion:
This interim analysis confirmed the safety of fNIRS-NFB in PD patients and suggested the beneficial effect on gait disturbance in PD patients.

Disclosures: M. Mihara: 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 Health and Labor Sciences Research Grants for Comprehensive Research on Persons with Disabilities (JP15652696) from the Japan Agency for Medical Research and Development (AMED), Grant in aid for S. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent pending: PCT2015065270/W2016189701. **H. Otomune:** None. **Y. Kajiiyama:** None. **H. Fujimoto:** None. **Y. Mitani:** None. **N. Hattori:** None. **Y. Watanabe:** None. **Y. Sunada:** None. **H. Mochizuki:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.05/R7

Topic: C.03. Parkinson’s Disease

Support: #NRCTR-EX18009

Title: Effect of robot-assisted gait training on gait automaticity in Parkinson's disease

Authors: *S. YUN[1], H. LEE[2], W. LEE[3], S. LEE[1], B.-M. OH[1], K. KIM[1], H. SEO[1]
[1]Dept. of Rehabil. Med., Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of; [2]Konkuk Univ. Med. Ctr., Seoul, Korea, Republic of; [3]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Gait automaticity is known to be reduced in patients with Parkinson's disease (PD) due to impaired habitual control. Robot-assisted gait training (RAGT) has been suggested to improve gait speed and balance in these patients. The aim of this pilot study was to investigate the effect of RAGT on gait automaticity as well as gait speed and balance in patients with PD. Patients with idiopathic PD (H&Y stage 2.5 or 3) received 12 sessions of RAGT, 45-min, 3 days a week, for 4 weeks using an exoskeleton-type gait robot with partial body weight support (Walkbot_S; P&S Mechanics, Seoul, Korea). Primary outcome was the percentage of dual-task interference measured by 10 meter walking test (10MWT) under single- and dual-task conditions. Cognitive dual-task walking was measured using Wechsler Forward Digit Span, and physical dual-task walking was measured with a tray with two cups of water. Patients were also evaluated with Berg Balance Scale (BBS) and Korean version of the Falls Efficacy Scale-International. All outcomes were measured before (T0), after (T1) and 1 month post-treatment (T2). Eleven patients with idiopathic PD were participated (Table 1). Cognitive dual-task interference was significantly increased at T1 (p=.026), but not at T2. No significant changes were found for physical dual-task interference at T1 and T2 (Table 2). Single-task gait velocity was significantly increased at T1 (p=.041), but not at T2 (p=.445). On the other hand, there were no significant changes in dual-task 10MWT. A significant improvement was also found on the BBS at T1 and T2 (p=.004 and p=.024, respectively). In this study, the gait automaticity in patients with PD was not improved by RAGT using an exoskeleton-type gait robot despite improvement in walking speed and balance. Additional therapeutic components may be needed to improve gait automaticity using RAGT in patients with PD.

Table 1. Patients' demographics and baseline characteristics (N=11)

Male/female (n)	5/6
Age (yr)	66.46 ± 5.66
Disease duration (mo)	112.91 ± 50.19
Hoehn & Yahr stage 2.5/3 (n)	8/3
MMSE-K (score)	28.55 ± 0.93

Mini Mental State Examination-Korea; MMSE-K

Table 2. Changes in percentage of dual-task interference (%)

		T0 (n=11)	T1 (n=11)	T2 (n=10)	Within-group comparisons (changes)	
					T1 - T0	T2 - T0
Gait velocity	Dual task (cognitive)	-15.78 (7.78)	-.21.50 (7.62)	-20.75 (6.40)	.026*	.203

	Dual task (physical)	-21.23 (7.42)	-21.10 (5.79)	-23.51 (12.55)	.929	.646

Percentage of dual-task interference; (dual-task performance – single-task performance)/single-task performance , T0; Before treatment, T1; After treatment, T2; 1 month post-treatment, †Mean (SD), *p<.05 by Wilcoxon signed-rank test

Disclosures: S. Yun: None. **H. Lee:** None. **W. Lee:** None. **S. Lee:** None. **B. Oh:** None. **K. Kim:** None. **H. Seo:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.06/R8

Topic: C.03. Parkinson’s Disease

Support: SAF2016-80647-R
SAF2017-86246-R
The Michael J. Fox Foundation 9205

Title: Abnormal motor cortex plasticity induced by transcranial static magnetic field stimulation in dyskinetic patients with Parkinson’s disease

Authors: M. DILEONE[1], C. AMMANN[1], V. CATANZARO[1], I. OBESO[1], A. OLIVIERO[2], J. A. OBESO[1], *G. FOFFANI[1,2]
[1]CINAC, Univ. Hosp. HM Puerta del Sur, Mostoles, Spain; [2]Hosp. Nacional de Parapléjicos, Toledo, Spain

Abstract: Levodopa-induced dyskinesias (LIDs) represent a common motor complication in Parkinson’s disease, but their pathophysiological mechanisms and even the exact brain circuits involved in their generation remain unclear. The aim of the present study was to test whether the primary motor cortex is just a ‘passive integrator’ of subcortical and cortico-cortical abnormalities, or it also plays an active role in the pathophysiology of LIDs. To address this issue, we adopted a new perturbation strategy, by applying transcranial static magnetic field stimulation (tSMS) of the motor cortex (Oliviero et al., J Physiol 2011; Dileone et al., Sci Rep 2017; Dileone et al., Brain Stimul 2018) in dyskinetic (n=22) and non-dyskinetic (n=17) patients with Parkinson’s disease. Crucially, all patients were studied off medication, after overnight withdrawal of dopaminergic therapy, when LIDs are absent in both groups. We assessed both corticospinal and intracortical tSMS-induced plasticity, using the amplitude of motor evoked potentials (MEPs) elicited by single-pulse transcranial magnetic stimulation (TMS) and short-interval intracortical inhibition (SICI) to paired-pulse TMS. In non-dyskinetic patients, 10-min-

tSMS induced MEP depression and increased SICI. In dyskinetic patients, conversely, 10-min-tSMS induced MEP potentiation and did not significantly modulate SICI. These results suggest that abnormal motor cortex plasticity may contribute to the pathophysiology of LIDs.

Disclosures: M. Dileone: None. **C. Ammann:** None. **V. Catanzaro:** None. **I. Obeso:** None. **A. Oliviero:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurek SL. **J.A. Obeso:** None. **G. Foffani:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurek SL.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.07/R9

Topic: C.03. Parkinson’s Disease

Title: Does high-cadence cycling promote changes in inhibitory brain circuits in Parkinson's disease?

Authors: *A. L. RIDGEL[1], Y.-C. CHUNG[2], J. HERSHBERG[3], C. BROWN[2], B. E. FISHER[3]
[1]Exercise Physiol., Kent State Univ., Kent, OH; [2]Keck Sch. of Med. of USC, Los Angeles, CA; [3]Div. of Biokinesiology and Physical Therapy, USC, Los Angeles, CA

Abstract: There is significant evidence for the benefits of exercise on motor symptoms in Parkinson’s disease (PD) and it has been suggested that exercise exerts its beneficial effects, at least partially, through changes in the brain. However, the exact nature of these alterations is not known and few studies have linked these changes in motor behavior with alterations of the brain. Transcranial magnetic stimulation (TMS) studies have documented both a decrease in cortical silent period duration (CSP) and short-interval intracortical inhibition (SICI) as common pathophysiological features in PD. Importantly, greater cortical inhibition after medication, as evidenced by an increase in CSP and SICI, has been associated with behavioral improvement. We have previously demonstrated that high-velocity treadmill training lengthened CSP and promoted improvements in gait in PD. We have also shown that high-cadence cycling increased brain activation as measured by fMRI and reduced motor symptoms in PD. These findings suggest that the high velocity component of these training paradigms may be the driver of these brain changes. However, it is not known if the velocity of movement drives the exercise-induced effects on motor performance by altering inhibitory circuits in the PD brain. In this exploratory study, individuals with mild-moderate PD were randomly assigned to either a high-cadence or a low-cadence dynamic cycling intervention, in which the pedaling rate varied around the target cadence. Participants cycled on a motorized stationary bike that maintained the identified cadence parameters 2-3 times per week for 3 months. At baseline and following the 3-month

intervention, single and paired pulse TMS was completed to determine the effect of cadence on CSP and SICI. TMS was applied to the more-affected motor cortex over the representational areas of tibialis anterior and first dorsal interosseous muscle. Preliminary analysis of the data showed no pre-post change in CSP in any of the participants. Interestingly, SICI was increased in all subjects regardless of cycling cadence. These results suggest that exercise facilitates beneficial brain changes in PD by modulating the inhibitory circuits, and that other components of dynamic cycling may be the key ingredients for enabling these changes. Future studies need to examine the role of cadence variability and rider motivation and consistent effort in identifiable brain changes after exercise.

Disclosures: A.L. Ridgel: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ridgel, Loparo, Discenzo, Abdar, "Bike System for Use in Rehabilitation of a Patient", US 9,802,081, 10/31/17. **Y. Chung:** None. **J. Hershberg:** None. **C. Brown:** None. **B.E. Fisher:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.08/R10

Topic: C.03. Parkinson’s Disease

Title: Comparison of deep brain stimulation lead impedance between Medtronic and St.Jude Medical/Abbott systems during the perioperative period

Authors: *E. L. HARGREAVES[1], N. A. BUCKLEY[2], D. O. CONNOLLY[2], D. L. CAPUTO[3], S. F. DANISH[4]
[1]Robert Wood Johnson Med. Sch. -- Rutgers Univ., New Brunswick, NJ; [2]Neurosurg., [3]Neurol., Robert Wood Johnson Med. Sch. - Rutgers Univ., New Brunswick, NJ; [4]Neurosurg., Cancer Insitute of New Jersey - Rutgers Univ., New Brunswick, NJ

Abstract: We measure stimulating lead impedance at final placement during Stage I implantations, again following connection of extensions and the neurostimulator during the Stage II implantations 7 days later and at the beginning of the contact screen prior to activation and every other programming session. The Medtronic Activa PC 37601 or ENS 37022 impedance measurements used endogenous parameters of 3.0V, 80µs, and 100Hz; 14 pulses per monopolar (against the neurostimulator case) or bipolar contact combination. The St.Jude Medical/Abbott (SJM) Infinity IPG models 6660 and 6662 and the ENS 6599 model used endogenous impedance parameters of 30µs, 250Hz, and 500µa cycling as necessary to 163µa, with one or two pulses. Individual contact impedance is measured against the aggregate of remaining contacts. The annular contacts of the both the Medtronic 3389 and 3387 leads and the annular contacts of the SJM 6172 and 6173 leads are 1.5mm in height by 1.27mm in diameter, composed of an 80/20

platinum/iridium mix. The Medtronic connecting wires are an identical alloy, embedded in a polyurethane insulation, whereas the SJM connecting wires are composed of a nickel cobalt alloy, embedded in ethylene tetrafluoroethylene, covered with Bionate hypo tubes (Michmizos et al., 2017). 52 leads from 26 individuals with Medtonic systems were compared to 15 leads from 8 individuals with SJM systems. Analysis of the monopolar contact impedances indicated that the Medtronic impedances (1002.22) were higher than the SJM impedances (627.24) for the Stage II ($F_{(1,353)}$=62.01; p=.0005) and Contact Screen (Medtronic 1381.20, SJM 1205.69; $F_{(1,353)}$=3.83; p=.051). No Left/Right or Dorsal/Ventral differences or interactions were observed.The SJM impedances decreased from Stage I to II then dramatically increased to the contact screen in a quadratic trend, regardless of the annular or segmented leads being tested ($F_{(1,52)}$=125.06; p=.0005). The Medtronic bipolar impedances exhibited the same quadratic pattern ($F_{(1,317)}$=84.84; p=.0005). The segmented contacts of the SJM recorded a higher impedance then their annular contacts (ann: 929.89 seg: 1672.43; $F_{(1,52)}$=215.85; p=.0005). Analogously, the bipolar contacts of the Medtronic system recorded a higher impedance than their annular contacts (ann: 1212.54 bi: 2017.27; $F_{(1,608)}$=473.70; p=.0005). Our initial analyses indicate that the perioperative impedances of both systems exhibit the same pattern across time, but that the SJM monopolar impedances are consistently less than the Medtronic monopolar impedances. This likely has to do with the impedance return anode using either the case versus the aggregate of the remaining contacts.

Disclosures: E.L. Hargreaves: 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.; Site PI for St.Jude/Abott PROGRESS study. **N.A. Buckley:** None. **D.O. Connolly:** None. **D.L. Caputo:** None. **S.F. Danish:** 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.; Consultant for Medtronic Laser induced Thermal Terapy.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.09/R11

Topic: C.03. Parkinson’s Disease

Title: Quantitative differences in white matter connections of DBS contacts and clinical outcome in Parkinson's disease

Authors: *V. E. RAGLAND[1], J. ARNEDO[2], J. TORANZO[2], M. J. USCAMAYTA AYVAR[2], A. C. MOLINA[2], G. A. DE ERAUSQUIN[2]

[1]Sch. of Med., Univ. of Texas Rio Grande Valley, Edinburg, TX; [2]Neurol. and Psychiatry, UTRGV Sch. of Med., Harlingen, TX

Abstract: Surgical planning and post-operative programming of deep brain stimulation (DBS) for Parkinson disease (PD) with motor fluctuations has changed relatively little over the past two decades and relies heavily on microelectrode recording and trial-and-error settings, respectively. Using probabilistic Diffused Tension Imaging (DTI) tractography followed by scheletonization and Tract-based spatial statistics (TBSS) we identified the connections of DBS leads in individual patients who underwent DBS surgery for Parkinson disease. We use these connections and clinical outcome data to predict characteristics associated with a favorable and unfavorable clinical response.
All subjects (n = 35) had MRI images as part of the surgical planning including FLAIR, contrasted T1,T2 and DTI images (64 directions) on a 3T Phillips scanner. Images were merged with the postoperative CT scan to identify the exact electrode placement. Following reconstruction, manual tracing of ROIs (involving the DBS lead active contacts) was performed on nonsegmented high resolution T1 images coregistered into T2 space with the post-op CT using BRAINLAB software (Feldkirchen, Germany). Images were realigned using the plane containing the anterior and posterior commissures and the sagittal sulcus to correct head tilt, and resampled into isotropic voxels (0.9375 mm3). Fractional anisotropy (FA) for each voxel was calculated for each volume. We developed a Generalized Factorization Method (GFM) to identify biclusters (i.e., subsets of subjects associated with a subset of particular characteristics, such as low FA in connections attached to each lead). Using the GFM, we identified characteristics associated with a favorable and unfavorable clinical outcome from DBS and programming data. The robustness (high/low FA values) and the destination of the white matter fibers (location) in the region of the active electrode are associated with favorable (high UPDRS-III scores) and unfavorable outcomes (low UPDRS-III) scores. The identification of patient clusters based on these characteristics allows response prediction and future treatment optimization.
o maximize efficacy and minimize the side effect profile for patients undergoing DBS surgery for Parkinson disease, DTI connectivity data can be used to predict and optimize clinical outcomes in future DBS lead placement and programming.

Disclosures: V.E. Ragland: None. **J. Arnedo:** None. **J. Toranzo:** None. **M.J. Uscamayta Ayvar:** None. **A.C. Molina:** None. **G.A. De Erausquin:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.10/R12

Topic: C.03. Parkinson’s Disease

Support: NIH T32MH020068
Doris Duke Charitable Foundation
Rhode Island Hospital Department of Neurosurgery

Title: Quantitative analysis of pneumocephalus-related brain shift in deep brain stimulation patients

Authors: *P. M. LAURO[1], A. M. ALDRIDGE[2], W. F. ASAAD[3]
[1]Dept. of Neurosci., [3]Neurosurg., [2]Brown Univ., Providence, RI

Abstract: Deep brain stimulation (DBS) is a therapy for movement disorders such as Parkinson's disease. Successful DBS outcomes depend on the precise placement of stimulating electrodes. When the skull is opened during the surgical procedure, CSF exiting the skull can be replaced by air. Resulting pneumocephalus can deform and shift the brain in a non-linear manner, potentially affecting the electrode placement accuracy and DBS clinical outcomes. Because movement disorders patients can be older, we also investigated the effect of age-related brain atrophy on pneumocephalus and resulting brain shift.

Thirty DBS patients received the following scans: preoperative T1-weighted (T1w) MR images, an intraoperative CT scan, and postoperative T1w MR images. All scans underwent linear skull-to-skull registration using a mutual information algorithm. Preoperative T1w images were segmented using Freesurfer. The resulting whole-brain volume was divided by the total intracranial volume. We then calculated an "atrophy index" by subtracting this ratio from 1. Voxels within CT images were segmented into different categories (blood, air, tissue) by Hounsfield values. The volume of "air" voxel clusters within the skull were calculated as the pneumocephalus volume. Finally, postoperative T1w images underwent nonlinear registration to preoperative T1w images. The resulting warp-field deformations in the medial-lateral, anterior-posterior, and dorsal-ventral axes were interpreted as "pre to post shift." The warp values in each dimension were collapsed into a single "vector shift" value, and each patient's "shift" value was an average of all "vector shift" voxels within the brain.

Pearson correlation of patient age and atrophy index revealed a non-statistically significant direct relationship ($r = 0.271$, $p = 0.147$). Patient atrophy index and pneumocephalus demonstrated a non-significant relationship ($r = -0.155$, $p = 0.414$). Similarly, pneumocephalus demonstrated a non-significant relationship with whole-brain shift ($r = 0.195$, $p = 0.301$). However, age and atrophy demonstrated statistically significant inverse relationships with whole brain shift ($r = -0.442$, $p = 0.014$; $r = -0.566$, $p = 0.001$).

While pneumocephalus does not appear to impact brain shift, increasing age and brain atrophy seem to decrease brain shift. This unexpected result may point to age-related changes in brain tissue compliance which are not measured with neuroimaging.

Disclosures: P.M. Lauro: None. **A.M. Aldridge:** None. **W.F. Asaad:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.11/R13

Topic: C.03. Parkinson's Disease

Support: GRAMMY Museum

Title: Effects of group singing on stress and motor symptoms in persons with Parkinson's disease

Authors: *E. L. STEGEMOLLER[1], A. F. ZAMAN[2], E. SHIRTCLIFF[1]
[1]Iowa State Univ., Ames, IA; [2]Kinesiology, Iowa State Univ. Dept. of Kinesiology, Ames, IA

Abstract: Research has revealed that group singing is an effective treatment strategy to improve respiratory control and muscle activity associated with swallow in persons with Parkinson's disease (PD). Moreover, singing groups can be enjoyable for participants and offer a way to relieve stress, have fun, and improve other motor symptoms. Thus, the purpose of this study was to examine the acute effects of group singing on stress and clinical measures of PD motor symptoms in persons with PD. Seventeen participants with PD (mean age = 76 ± 7 years; 47% male; disease duration = 7 ± 5 years) that engage in weekly group singing completed the study. Participants were tested on medication and had been singing in the group for a mean of 2.4 ± 1.4 years. Self-report and physiological data were collected prior to and after 1 hour of therapeutic group singing. The Unified Parkinson's Disease Rating Scale (UPDRS) was collected to assess the clinical motor symptoms and later scored by a trained rater blinded to pre/post collection. Subjective measures anxiety, sadness, happiness, and anger were also collected to measure emotion and affect. Heart rate, blood pressure, and salivary cortisol provided an index of physiological stress. Saliva samples were frozen within 1 hour of collection and stored at -80^{o}C. Saliva was thawed and assayed in duplicates using a commercially-available enzyme-immunoassay (Salimetrics, LLC). Results revealed that participants subjectively felt less anxious (p = 0.05) and less sad (p = 0.002) after the singing group. There were no significant differences in happiness or anger. Heart rate, blood pressure, and cortisol levels were also reduced, but did not reach significance. Lastly, motor symptoms significantly improved (p = 0.026), which was driven mostly by improvements in upper extremity bradykinesia, tremor, and walking. These results suggest that singing may have benefits beyond improving respiratory control and swallow in persons with PD, improving mood and motor symptoms as well as reducing physiological indicators of stress. Thus, group singing holds promise as an alternative treatment strategy for persons with PD that has a broad impact on motor symptoms, stress, and quality of life.

Disclosures: E.L. Stegemoller: None. **A.F. Zaman:** None. **E. Shirtcliff:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.12/R14

Topic: C.03. Parkinson's Disease

Title: A retrospective analysis of chronic STN LFP beta signals recorded by the Medtronic Activa® PC+S implanted in Parkinson subjects

Authors: M. CASE[1], S. STANSLASKI[1], V. VASOLI[1], J. XIAO[1], S. GOETZ[1], T. DENISON[1], *R. S. RAIKE[2]
[1]Medtronic, Minneapolis, MN; [2]Medtronic Inc, Minneapolis, MN

Abstract: Deep brain stimulation (DBS) is an approved therapy for treating the motor symptoms of Parkinson disease (PD). Several long-term follow-up studies demonstrate the safety and efficacy of subthalamic nucleus (STN) DBS for PD, though improvements could facilitate increased adoption among eligible patients. Closed loop or adaptive DBS algorithms are emerging as a promising approach for individualizing and optimizing the therapy. Perhaps the most commonly-used control signals promising chronic accessibility for adaptive DBS (aDBS) are local field potentials (LFPs), representing oscillations in neuronal network activity adjacent to the recording electrode. LFP beta band (13-30 Hz) power can be associated with different PD patient states, including symptom, therapy and disease progression. For example, PD bradykinesia, rigidity and gait freezing are associated with high-amplitude, long-duration STN LFP beta oscillations, which are distinct from the beta activity associated with normal movements. Both PD medication and DBS therapies suppress pathological LFP beta band power while improving both bradykinesia and rigidity but not tremor. Furthermore, a growing body of evidence from independent research groups suggests potential efficacy, side-effect and efficiency benefits to LFP-beta controlled STN aDBS in studies of akinetic-rigid PD subjects. However, the broad translational potential of LFP beta aDBS is still debated, particularly with respect to general accessibility of sufficient control signals. Critically, LFP signals have been demonstrated to be chronically accessible and stable for years when recorded with the same DBS electrodes that deliver therapy. Although some single-center studies report high rates of success detecting robust LFP beta signals within the PD STN, replicability of this result is an important question. Therefore, we conducted a retrospective analysis of chronic STN LFP beta signals recorded from a large multi-center cohort of PD subjects implanted with the Medtronic Activa® PC+S, which is an investigational device capable of both delivering standard electrical stimulation therapy and recording LFP data through DBS therapy leads. The relationship between LFP beta signal strength and DBS lead location within the brain and PD phenotype (tremor dominant, akinetic-rigid or mixed) will be explored.

Disclosures: **M. Case:** A. Employment/Salary (full or part-time):; Medtronic. **S. Stanslaski:** A. Employment/Salary (full or part-time):; Medtronic. **V. Vasoli:** A. Employment/Salary (full or part-time):; Medtronic. **J. Xiao:** A. Employment/Salary (full or part-time):; Medtronic. **S. Goetz:** A. Employment/Salary (full or part-time):; Medtronic. **T. Denison:** A. Employment/Salary (full or part-time):; Medtronic. **R.S. Raike:** A. Employment/Salary (full or part-time):; Medtronic.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.13/R15

Topic: C.03. Parkinson's Disease

Support: Shake It Off, Inc. 501(c)(3)

Title: Pilot study on the interaction between exercise, medication, and Parkinson's disease symptoms

Authors: *S. L. HOWARD, C. A. KNIGHT
Univ. of Delaware, Newark, DE

Abstract: Motor symptoms of Parkinson's disease (PD) include tremor, bradykinesia (slow movement), rigidity and impaired postural control. Symptoms are treated with dopamine replacement therapies (DRT) and it has been shown that exercise helps slow disease progression and improve mobility. In studies involving rapid isometric contractions, some have reported abnormally segmented force production that could impair multiple aspects of mobility. There has been little development of segmentation measures. Aim 1 was to explore the interaction between single bouts of speed-based exercise and DRT in the management of bradykinesia during the later-day 'wearing-off' phase when DRT doses sometimes have diminished efficacy. Grip strength, timed up and go (TUG) and isometric force pulses were measured before and after three treatment conditions: 1) no exercise, DRT only; 2) no DRT and a 30-minute high-speed low resistance (HS-LR) bicycling session; and 3) DRT plus HS-LR bicycling session in nine subjects with PD (Hoehn-Yahr $\leq$ 3.0). It was hypothesized that the medication plus exercise condition would cause the greatest improvement in function. Aim 2 was to evaluate test-retest reliability of force segmentation and time to peak force (tPF) measures. Paired t-tests did not support any treatment effects (all p>.186). T-statistics were greatest in the medication-only condition for grip strength (t=1.39, p=.202) and force segmentation (t=1.447, p=.186), in the direction of improvements. Delaying an afternoon dose of medication was more challenging for some subjects. Individual exercise responses varied considerably. Segmented force pulses were observed in most subjects and the mean segmentation was strongly correlated with tPF on all three visits (r=.879-.961) suggesting that slowing in force production is related to a disruption, rather than a reduction, in neural drive. ICCs supported favorable test-re-test reliability of mean

segments (r=.83) and tPF (r=.82) relative to ICCs of .96 and .82 for grip strength and TUG, respectively. The methodological approach to Aim 1 would likely require a larger sample size and better control of confounding variables to determine, with adequate power, whether afternoon exercise can boost function alone or with medication. Results related to Aim 2 are promising in that mean segmentation has similar reliability to TUG, which is already accepted in rehabilitation research. Furthermore, strong correlations between segmentation and tPF support further inquiry into the role of disrupted neural drive in bradykinesia.

Disclosures: S.L. Howard: None. **C.A. Knight:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.14/R16

Topic: C.03. Parkinson’s Disease

Support: NINDS Intramural Research Program

Title: Tractography-based machine learning algorithm for prediction of acute stimulation-induced side effects in DBS for Parkinson's disease

Authors: *S. C. NANIVADEKAR[1], P. TAYLOR[2], D. EHRLICH[1], C. LUNGU[1], S. G. HOROVITZ[1]
[1]NINDS, [2]NIMH, NIH, Bethesda, MD

Abstract: Deep Brain Stimulation (DBS) is an invasive treatment that improves motor symptoms in Parkinson disease. Certain DBS settings can lead to acute side effects like paresthesia, facial pulling, or speech difficulty, and need to be avoided. Using diffusion tensor imaging (DTI) and clinical data, we have developed a tractography-based algorithm to classify SideEffect (SE) vs. non-SideEffect (nSE) DBS settings. We included neuroimaging and clinical data from 33 Parkinson’s patients with subthalamic nucleus DBS and 6 patients with globus pallidus DBS. T1-, T2-, and Diffusion- weighted images were collected pre-Operatively and T2w images and CT scans were collected post-Operatively. Diffusion data was preprocessed in TORTOISE[1]. We modeled patient-specific volumes of tissue activated (VTA) using DBSproc[2] for the stimulation parameters on each contact that produced clinical benefit (entry) and acute sensorimotor side effects (exit). We performed probabilistic tractography to determine the white matter connectivity between the grey matter ROIs defined from Freesurfer segmentation plus subcortical areas in the ventral diencephalon. We identified tracts that intersected with the VTA at the entry and exit voltages, and computed a binary connectivity vector (intersects with a given tract or not). Each contact and setting had an associated label (SE or nSE). We then used a logistic regression-based single-layer neural network to train the algorithm to classify an

unlabeled connectivity vector into one of the two output classes. The percent error of the training dataset was 37.61% and the testing dataset was 28.72%. The ranked weight vector of the hidden layer in the classifier provided us with the tract features that were most important to determining the output class of the connectivity pattern. Tracts emanating from the L. thalamus to the brainstem, amygdala and putamen were most important in being able to classify the groups. We also performed a voxel-wise t-test on the connectivity maps to find differences between the symptom-producing contacts and the non-symptomatic contacts. Areas in the L. thalamus, putamen and brainstem showed significant ($p<0.005$) differences, providing empirical validation for our learning algorithm. Hence, we developed an effective algorithm that can predict, for a contact and stimulation setting, the probability of side effect occurrence based on the connectivity profile of the stimulation. This learning algorithm allows us to identify biologically relevant tracts that, if selectively stimulated, may generate undesirable side effects.
References:
[1]Pierpaoli, et al., *ISMRM* (2010)
[2]Lauro et al. *Human Brain Mapping* (2016)

Disclosures: S.C. Nanivadekar: None. **P. Taylor:** None. **D. Ehrlich:** None. **C. Lungu:** None. **S.G. Horovitz:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.15/R17

Topic: C.03. Parkinson’s Disease

Support: NIH-NINDS R01NS673717

Title: Alterations in the control and coordination of grasping forces in Parkinson’s disease following aerobic exercise

Authors: *J. L. ALBERTS[1], A. PENKO[2], A. E. JANSEN[2]
[1]Biomed. Engin., [2]Dept. of Biomed. Engin., Cleveland Clin., Cleveland, OH

Abstract: For individuals with PD, motor control impairments may have a substantial impact on overall dexterity and consequently on activities of daily living. Aerobic exercise has been shown to be a beneficial adjunctive therapy to standard clinical care for individuals with Parkinson’s disease (PD), and has resulted in global motor function improvements. However, the effects of lower extremity exercise on the control and coordination of grasping forces during bimanual dexterous actions is unknown. The aim of this project was to determine the effects of high-intensity aerobic exercise on changes in bimanual force coordination patterns in individuals with PD. A total of 26 PD patients completed a supervised eight week (3x per week) high intensity

aerobic exercise intervention. Grasping forces and torques were measured during the completion of a bimanual dexterity task in which one limb served to stabilize the object while the other limb performed a manipulation action. Dexterity assessments were completed at baseline both “on” and “off” PD medications, end of treatment (EOT), and EOT + 8 weeks (EOT+8). Overall, the participants were compliant with the prescribed exercise protocol. Results from the dexterity task indicated that, compared to baseline off conditions, following exercise there was an improvement in total task time. Improvements in task time were likely the result of improved rate of grip force production, improved bilateral onset of grip and load forces and enhanced coordination of grip-load coupling. Enhanced bimanual dexterity in PD patients, following aerobic exercise, suggest that exercise may be altering the mode of force control as PD patients may be shifting from a reliance on feedback to feedforward control patterns. An improvement in the specification of upper extremity forces, following a lower extremity exercise intervention, indicates high intensity aerobic exercise results in a global improvement in central nervous system functioning.

Disclosures: J.L. Alberts: None. **A. Penko:** None. **A.E. Jansen:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.16/R18

Topic: C.03. Parkinson’s Disease

Title: Food consumption and serum indicators of oxidative stress in patients with early-stage Parkinson's disease: A pilot study

Authors: *M. NAVARRO MEZA, SR[1], M. OROZCO-IBARRA[2], E. MORALES-SANCHEZ[3], F. PACHECO-MOISES[4], E. BECERRA-HERNÁNDEZ[5], F. SANTOYO-TELLES[5], G. GABRIEL ORTIZ[6]
[1]Ctr. Universitario del Sur/ Univ. de Guad, Ciudad Guzman, Mexico; [2]Lab. of Mol. and Cell. Neurobiology,, National Institute of Neurology and Neurosurgery, Mexico; [3]Dept. of Hlth. Sci., University of Guadalajara, Mexico; [4]Dept. of Chemistry. Univ. Ctr. of Exact and Engin. Sciences., University of Guadalajara., Mexico; [5]Ctr. Univ. of South., University of Guadalajara. México, Mexico; [6]Div. of Neurosciences., Occidental Biomedical Research Centre, Social Secu, Mexico

Abstract: Oxidative stress (OS) constitutes one of the earliest alterations of Parkinson’s disease (PD) and recent data suggest that dietary intake influences the risk of developing this disease. Thus, studies about the nutrient intake and its relationship to OS in PD may provide information that will help to make nutritional recommendations. We evaluated food intake, OS markers and antioxidant activities of patients in early stages of PD. A cross-sectional, descriptive, and comparative study in early-stage PD patients and controls was conducted. A sample of 22 adults

with an age range of 43-88 years was included in order to match controls and PD patients. All participants received detailed information about the study and signed a letter of informed consent. This investigation was performed according the Declaration of Helsinki and the Regulations of the General Health Act of Mexico. Methodological procedures were approved by the Ethics and Research Committee of the of the Health Department in Jalisco. Additionally, the integrity and security data of PD patients and adults without neurodegeneration included in the study were protected. Anthropometric measurements, food consumption, lipid peroxidation products, carbonylated proteins, total antioxidant capacity and enzymatic activities of catalase, superoxide dismutase and glutathione peroxidase were assessed. The blood sampling and analyses were performed in coordination with the Regional Hospital of Ciudad Guzman in Jalisco, Mexico. Descriptive statistics including the mean and standard deviation were used in patients' sociodemographic characteristics and food consumption frequency. To determine statistically significant differences in biochemical indicators between patients and the control group, a student-T test and distribution was used. For the chemical variables, the Kolmogorov-Smirnov test was used to confirm the normality. PD patients showed a higher intake of monounsaturated and saturated fatty acids ($p<0.05$) than controls; in addition, levels of lipid peroxidation products and catalase activity were increased in PD patients compared to controls ($p<0.05$). These results together with the low intake of antioxidant vitamins A, E and folic acid, suggest alterations in oxidative status in PD patients; however, further studies are required with a larger sample of patients including patients with other stages of PD.

Disclosures: M. Orozco-Ibarra: None. **E. Morales-Sanchez:** None. **F. Pacheco-Moises:** None. **E. Becerra-Hernández:** None. **F. Santoyo-Telles:** None. **G. Gabriel Ortiz:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.17/S1

Topic: C.03. Parkinson's Disease

Support: CONACYT STUDENT GRANT 828866

Title: Burden and caregiving in Parkinson's disease due to apathy

Authors: *J. G. AVILA-LORETO[1], M. ARROYO-MEDRANO[2], T. VILLASEÑOR-CABRERA[2]
[1]Univ. De Guadalajara, Guadalajara, Mexico; [2]Univ. de Guadalajara, Guadalajara, Mexico

Abstract: Background: It has been shown that the risk of burden in caregivers of people with Parkinson's disease (PD) is increased when affective symptoms predominate. The most studied are related to depression, however the relationship between the burden of the caregiver and the

levels of apathy of the patient is unknown. Objective: This study aims to evaluate the burden and associated factors on caregivers of people with PD who show apathy. Methods: An observational, cross-sectional study was carried out with 25 pairs of caregivers and their patient from the Clinic of Abnormal Movements and Neurodegenerative Disorders from the Fray Antonio Alcalde Civil Hospital. They were assessed using the Zarit burden inventory (ESCZ) and the Starkstein Apathy Scale (AS) respectively. The overall proportions of each scale were analyzed with Student's T for independent samples and Pearson correlation. Results: Preliminary, 50 participants, 25 caregivers (mean age 52.6 ± 13 years) and their patients (65.1 ± 11 years) were enrolled. The majority of caregivers were providing assistance to the patient for ≥ 4 years, caregiving 12 h a day. Most caregivers were spouses. Female caregivers were more overburdened (56%) than male caregivers (22%). Overall score in ESCZ was correlated with the presence of apathy in patients with PD (p= 0.372) mainly in the domain of caregivers personal and social life deterioration. Conclusions: The levels of burden in caregivers correlate with levels of apathy in patients with PD. We also found that they are more women who are responsible for care and have a higher level of overload than men.

Disclosures: J.G. Avila-Loreto: None. **M. Arroyo-Medrano:** None. **T. Villaseñor-Cabrera:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.18/S2

Topic: F.01. Neuroethology

Support: CNPq Grant 870322/1997-4
CNPq Grant 307967/2015-8

Title: Effects of the manipulation of an artwork on time perception in Parkinson’s disease patients

Authors: *J. O. BUENO[1], M. R. MOTTA[2], V. TUMAS[3]
[2]Psychology, [3]Neurosci. and Behavior, [1]Univ. São Paulo, Ribeirao Preto, Brazil

Abstract: Introduction: Different situations and conditions can alter the temporal perception of individuals, for instance, the artworks appreciation by Parkinson’s disease (PD) patients. It is known that PD is characterized by a dysfunction of the dopaminergic system that is considered involved in temporal processing and motor function. The appreciation of artworks through manipulation can alter the perception of the time of people with this disease. Objective: Examine how the manipulation of artworks affects time perception in PD patients. Methods: The research ethics committee of the University of São Paulo approved the study and the informed consent

was collected from all participants prior to the test. Ten participants with PD and 10 healthy subjects were required to manipulate two reproductions of artworks from the series “Bichos” by Lygia Clark (1960) with different number of piece (six piece: less complex-LC; ten piece: more complex-MC). After that, they performed a verbal estimation about the temporal duration of their manipulations. The behaviors were recorded and then transcribed and analyzed. The data were analyzed by Shapiro-Wilk, Mann-Whitney U and Wilcoxon tests. Results: All participants overestimated the manipulation time of the artworks. However, participants with PD showed less overestimation than healthy subjects. The manipulation time of the artworks to PD patients was shorter than to the healthy subjects and PD patients showed a lesser time of manipulation of the MC artwork. Four behavioral categories were analyzed: Touch, Move, Change of the artwork’s placement and Release the piece of art. The analysis of the exploratory activity of the participants showed that those with PD touched and released the stimulus more often and, in contrast, they moved and dislocated it less than the participants without the disease. PD participants presented a greater proportion of touches to MC artwork and lesser frequently of movement to LC artworks than to healthy subjects. Conclusion: PD patients showed altered perception of artwork manipulation time. This suggests that exploratory behavior influenced temporal estimation. In addition, it is possible that patients with PD had decreased ability to manage attention during the task, that interfered in the cognitive reconstruction of its duration. These considerations indicate that, as a result of cognitive and motor changes, patients with PD present impaired temporal information processing. The involvement of exploratory behavior facilitated the understanding of these results and processes in terms of timing operations of the basal-talocortical ganglion system.

Disclosures: J.O. Bueno: None. **M.R. Motta:** None. **V. Tumas:** None.

Poster

656. Parkinson's Disease: Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 656.19/S3

Topic: E.07. Rhythmic Motor Pattern Generation

Support: JUMP-ARCHES

Title: A personalized neuromechanical simulation of hand pronation and supination task in persons with parkinson’s disease: Effects of tonic dopamine levels and disease progression

Authors: *L. ZIEGELMAN[1], Y. HU[2], R. SUN[3], M. E. HERNANDEZ[2,1]
[1]Neurosci., [2]Kinesiology and Community Hlth., [3]Mol. and Cell. Biol., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: This study aimed to create a neuromechanical simulation of hand pronation and supination. This was accomplished by combining an adapted Matsuoka oscillator and torque-based equations to model the kinematics of the desired motion. In addition to the exploration of changes in neural and biomechanical conditions due to age and presence of a neurodegenerative disorder such as Parkinson's Disease, this model aims to accurately simulate changes in a patient's ability to pronate and supinate their hand based off their access to medication and disease progression. Healthy young adults (HYA), healthy older adults (HOA), and patients with Parkinson's Disease (PD) performed 5 trials of repeated pronation and supination for 30 seconds while wearing an InertiaCube BT. This experimental data was used to validate the position output of the model. This simulation shows marked decreases in amplitude and frequency of movement with the progression of PD as well as during the off-medication phase. This simulation is the first to recreate pronation and supination kinematics based on changes in descending or tonic input due to disease progression.

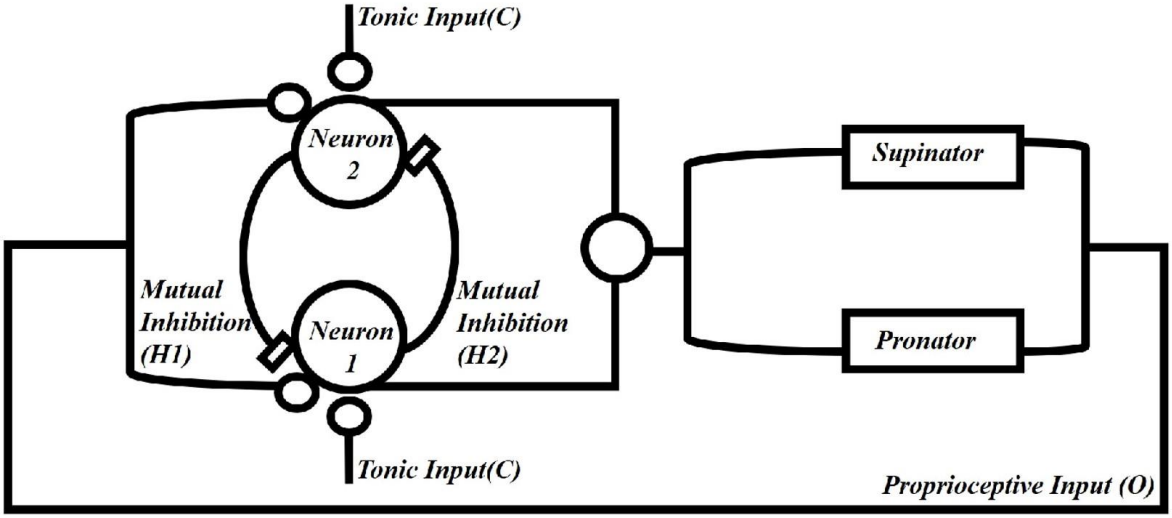


Fig. Representation of the model proposed for hand pronation and supination. This model includes two mutually inhibitory neurons forming a central pattern generator that results in pulses to the supinating and pronating muscles of the hand. The tonic input received by each neuron represents the descending input from the brain, altered by the severity of Parkinson's Disease and the medication state of the individual. Proprioceptive input from the hand is received by the central pattern generator when the hand pronates or supinates past its natural range of motion.

Disclosures: L. Ziegelman: None. **Y. Hu:** None. **R. Sun:** None. **M.E. Hernandez:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.01/S4

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Field Neuroscience Institute
Office of Graduate Studies at Central Michigan University

Title: Mutant Huntington gene-silencing through CRISPR-Cas9 restores the mitochondrial biogenesis in in-vitro model of Huntington's disease

Authors: *N. KOLLI[1], M. LU[2], P. MAITI[4], J. ROSSIGNOL[5], G. L. DUNBAR[3]
[1]Neurosci., Central Michigan Univ., Nellore, India; [2]Neurscience, Central Michigan Univ., Mount Pleasant, MI; [3]Neurosci., Central Michigan Univ., Central Michigan University, MI; [4]Psychology and Neurosci. Program, Central Michigan University/St. Mary's of Michigan, Saginaw, MI; [5]Field Neurosciences Inst. Lab., Mount Pleasant, MI

Abstract: Huntington’s Disease (HD) is a rare autosomal dominant neurodegenerative genetic disorder, resulting in abnormal movements of the limbs, along with cognitive deficits and psychiatric symptoms. The underlying cause of the disease is a genetic mutation of the *huntingtin* gene (m*HTT*), which codes for the huntingtin protein (HTT), whereby the poly-glutamine (CAG) repeat domain is extended to more than 35 CAG repeats. Though exact mechanism of the HD pathology is not known, several studies reported abnormal mitochondrial dynamics in HD patients, HD mouse models, and cell lines that express mutant Htt. CRISPR-Cas9 plasmid was constructed to target the DNA at untranscription region (UTR) upstream to the open reading frame (uORF) that resulted in 79 percent decrease in the mutant mHTT protein in the bone marrow derived mesenchymal stem cells (BM MSCs) extracted from YAC128 that carry human mutant huntingtin protein. CRISPR-Cas9 editing leads to indel mutations (random addition / deletions of nucleotides) at the targeted site. This enabled us to obtain single cell clones that expressed different levels of mutant huntingtin protein. The goal of this study was to unravel the link between toxicity exerted by mutant huntingtin and mitochondrial dysfunction. We have observed that blocking the mHTT by CRISPR-Cas9 increased the cell survival of the BM MSCs and restored abnormal mitochondrial bioenergetics involved in HD progression.
Key Words: Huntington’s Disease, CRISPR-Cas9, gene-silencing, mitochondrial bioenergetics.

Disclosures: N. Kolli: None. **M. Lu:** None. **P. Maiti:** None. **J. Rossignol:** None. **G.L. Dunbar:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.02/S5

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI (A-12457 to R.G.)
German Research Council (Exc 257/ to RG)

Title: Comparison of the effects of PHP.eB vectors encoding truncated or point-mutated EAAT2 isoforms as opposed to wild-type EAAT2 in single striatal astrocytes of Q175 heterozygote mice

Authors: *S. HIRSCHBERG[1], A. DVORZHAK[1], S. ANGELOV[1], P. KOVERMANN[2], R. GRANTYN[1]
[1]Einstein Ctr. for Neurosciences, Charité Univ. Med. Berlin, Berlin, Germany;
[2]Forschungszentrum Jülich, Institute of Complex Systems, Germany

Abstract: Neurodegenerative diseases such as Huntington's disease (HD), Alzheimer's disease and ALS are often associated with a reduced expression of the astrocytic glutamate transporter EAAT2 (GLT1 in rodents) and, consequently, ineffective clearance of glutamate from the perisynaptic space. This may contribute to excitotoxic damage. Earlier attempts in our lab to restore normal glutamate uptake by treatment with the transcription activator ceftriaxone or by intravenous injection of AAV9/PHP.B gfaABC1D-GLT1-P2A-Tomato in the Q175 mouse model of HD failed to produce substantial benefits with regard to the respective motor symptoms. The aim of the present study in symptomatic Q175 heterozygotes (15-18 months at sacrifice) was to determine the effects of 3 new PHP.eB-EAAT2 vectors with regard to the achieved levels of EAAT2 immunofluorescence, glutamate uptake activity and motor performance (escape latency). All vectors are stereotaxically injected into the dosal striatum at a concentration of 10 ^ 12 gc/ml. Astrocytes are specifically targeted by using the gfaABC1D promoter. Transduced astrocytes are identified by YFP fluorescence. We compare the expression and effects of the full-length EAAT2 sequence, a C-terminal-truncated EAAT2-sequence and a sequence with point mutations of lysine residues (K517R, K526R, K550R, K570R) that prevent ubiquitin-mediated internalization. Using confocal optics, the level of EAAT2 protein is determined within the territory of individual transduced astrocytes (YFP+) and in the immediate neighborhood of vGluT1+ and vGluT2+ presynaptic terminals within the YFP+ territory. Glutamate uptake activity is elicited by single-cell glutamate uncaging and recorded by SBFI imaging of respective sodium transients in transduced astrocytes. Animals injected with identical vectors but lacking the EAAT2 sequence served as controls. As a result of our current work in progress, we should be able to determine whether PhP.eB constructs containing the truncated or point-mutated EAAT2 isoforms can outperform vectors with the wild-type EAAT2.

Disclosures: S. Hirschberg: None. **A. Dvorzhak:** None. **S. Angelov:** None. **P. Kovermann:** None. **R. Grantyn:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.03/S6

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH-R03 NS084386
NIH- R03 NS092024

Title: Evidence for the axonal transport of a HTT-RAB4 vesicle complex which is disrupted in Huntington's disease

Authors: *S. GUNAWARDENA[1,2], J. WHITE[2], H. HOFMAR-GLENNON[2], C. THANT[2], K. ZIMMERMAN[2], G. IACOBUCCI[2]
[1]Dept. of Biol. Sci., SUNY at Buffalo, Buffalo, NY; [2]The State Univ. of New York at Buffalo, Buffalo, NY

Abstract: The Huntington's disease (HD) protein, HTT associates with molecular motors, however, the cargo complex that HTT moves within axons remains elusive. Previously, we found that HTT differentially regulated the motility of a sub-set of small GTPase Rabs. While Rabs are restricted to particular cellular compartments, the localization of one of these HTT-mediated Rabs, Rab4 is unknown. Here, we tested the hypothesis that a synaptic HTT-Rab4 moving complex exists *in vivo* and that scaffolding proteins present on this complex mediate associations between this complex and motors during axonal transport. Simultaneous dual-view imaging in larval axons revealed that HTT and Rab4, and Rab4 and SYNT/SYNB co-migrate within axons. Co-localization analysis showed that Rab4, HTT and motors co-localize in *Drosophila* and human neurons. Intriguingly reduction of the huntingtin interacting protein 1 (HIP1) and a known Rab effector, Rip11, perturbed both HTT and Rab4 motility *in vivo*. In both mouse and human neurons, Rab4 and HIP1 were present on membranes, while kinesin and HIP1 co-IPed on Rab4 membranes. RIP11 and Rab4 were also co-localized within larval axons, indicating that HTT-Rab4-HIP1-RIP11 and motors likely form a complex during axonal transport. Strikingly, Rab4 motility was disrupted during HD in both Drosophila and human neurons differentiated from HD patients. Larvae expressing polyQ HTT or neurons derived from HD patients exhibited axonal blockages that contained HTT, Rab4 and motors. Collectively, our observations suggest that a moving HTT-Rab4 complex exists and that HIP1 and Rip11 function as scaffolding proteins to link this complex to motors for proper axonal transport. Our findings have important implications for how defects in Rab4 motility contribute to HD.

Disclosures: S. Gunawardena: None. **J. White:** None. **H. Hofmar-Glennon:** None. **C. Thant:** None. **K. Zimmerman:** None. **G. Iacobucci:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.04/S7

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Investigating the role of aging in Huntington's disease pathogenesis

Authors: *E. MACHIELA[1], M. SCHMIDT[3], N. S. CARON[4], S. MEHTA[5], V. B. MATTIS[6], A. L. SOUTHWELL[2]
[1]Burnett Sch. of Biomed. Sci., [2]Col. of Med., Univ. of Central Florida, Orlando, FL; [3]Neurosci., Univ. of British Columbia, Vancouver, BC, Canada; [4]Med. Genet., Ctr. for Mol. Med. and Therapeut., Vancouver, BC, Canada; [5]Cedars-Sinai, Los Angeles, CA; [6]Board of Governors Regenerative Med. Inst., Cedars-Sinai, West Hollywood, CA

Abstract: Huntington’s disease (HD) is an autosomal dominant disease caused by a CAG repeat expansion in exon 1 of the huntingtin gene. HD is characterized by loss of voluntary movement, neuropsychiatric abnormalities, and cognitive decline. There are currently no disease-modifying therapies for HD. While age of onset negatively correlates with CAG repeat tract length, this only accounts for some of the variation in age of onset of disease. Many other genetic and environmental factors play a role in disease onset. Apart from juvenile-onset HD, which is caused by very long expansions of the CAG repeat tract, carriers of the mutation that causes HD live asymptomatically until mid-life, begging the question of how the aging process may contribute to onset of disease. Accelerated markers of aging such as DNA methylation have been shown to be present in brains of patients with HD. Additionally, cellular functions that decline during the aging process, such as the stress response and functions of the proteasome and mitochondria undergo rapid decline in HD, further supporting the hypothesis that aging contributes to HD pathology.
To investigate the role of aging in HD, we will useare using induced pluripotent stem cell (iPSC)-derived neurons from HD patients as well as healthy controls. One hurdle in the development of disease-relevant iPSC models of HD is the fact that during cellular reprogramming, cells lose markers of age. Further supporting the notion that aging plays an active role in HD pathogenesis, iPSC-derived adult onset HD neurons exhibit very mild phenotypes and no spontaneous neurodegeneration. To overcome this, we will treat HD and control cells with progerin, a truncated protein created by alternative splicing of the *LMNA* gene. Accumulation of progerin causes Hutchinson-Gilford progeria, a disease of rapid aging. Progerin has also been found in healthy tissues during the aging process and has been linked to cellular senescence. Additionally, iPSC-derived neurons treated with progerin exhibit markers of aging, suggesting a role for progerin in physiologic aging. Treating iPSC-derived HD neurons with progerin can unmask cellular phenotypes of HD related to the aging process. In doing this, we

can compare cellular phenotypes in HD neurons that are physiologically “young” and “old” but chronologically identical, to determine the role of physiologic aging in the cellular toxicity of HD. Ultimately, this work will shed light on aging-associated factors that contribute to HD pathogenesis to uncoverand whether anti-aging treatments that may be beneficial for HD patients.

Disclosures: E. Machiela: None. **M. Schmidt:** None. **N.S. Caron:** None. **S. Mehta:** None. **V.B. Mattis:** None. **A.L. Southwell:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.05/S8

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CIHR grant MOP-84438
Brain Canada and HSC grant
HDSA grant
CIHR postdoctoral fellowship
James family postdoctoral fellowship
HDSA summer fellowship

Title: HTT lowering-mediated changes in cerebrospinal fluid mutant huntingtin concentration: What does it mean?

Authors: *A. L. SOUTHWELL[1], N. S. CARON[2], C. YANICK[1], Y. XIE[1], S. E. SMITH[3], J.-J. SONG[4], I. SEONG[5], B. R. LEAVITT[2], M. R. HAYDEN[2]
[1]Col. of Med., Univ. of Central Florida, Orlando, FL; [2]Ctr. for Mol. Med. and Therapeut., Univ. of British Columbia, Vancouver, BC, Canada; [3]Ctr. for Integrative Brain Res., Seattle Childrens Res. Inst., Seattle, WA; [4]Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Democratic People's Republic of; [5]Molec Neurogenetics, Massachusetts Gen Hosp, Boston, MA

Abstract: The first huntingtin (HTT) lowering Phase I/2a clinical trial was recently completed, demonstrating dose-dependent reduction of CSF mutant (mt)HTT protein in response to treatment. However, there is very little known about CSF mtHTT; where it comes from or how it enters CSF. Thus, interpretation of these treatment-induced changes is not straightforward. We are using our ultrasensitive immunoprecipitation and flow cytometry (IP-FCM) mtHTT detection assay to better understand what this exciting new data tells us about therapeutic activity in the brain. The source of CSF mtHTT is unknown. The agent under trial is expected to be most active in regions in close contact with the CSF. If these regions are also the major sources of CSF mtHTT protein, then predictions of HTT lowering in deeper structures based on CSF findings

may not be accurate. Conversely, if regional contributions to CSF mtHTT protein are similar in deep and superficial structures, then changes in CSF mtHTT level could be used to infer changes to basal ganglia mtHTT. Thus, we are interrogating the source(s) of CSF mtHTT protein using BACHD HD model mice (floxed mtHTT exon 1) crossed to brain region and cell type-specific cre mice. These crosses generate mice with selective inactivation of mtHTT to enable evaluation of the contribution of the different brain regions or cell types to the pool of CSF mtHTT protein. Additionally, we do not know how mtHTT enters CSF. If it is released passively from dying cells, any neuroprotective therapy would be expected to reduce CSF mtHTT, and the treatment-induced changes observed in the current trial may represent a combination of HTT lowering and neuroprotection. Conversely, if active clearance is primary mechanism of mtHTT release to CSF, then treatment-induced changes may only represent HTT lowering. We have previously shown that mtHTT is not detected in CSF of all premanifest HD mutation carriers and that acute brain injury causes a transient increase in CSF mtHTT, suggesting that mtHTT is passively released from dying cells. However, we have observed mtHTT in the CSF of mice without neurodegeneration and reduced CSF mtHTT in BACHD mice lacking astrocytic mtHTT, suggesting that there may be both passive and active clearance mechanisms involved. We are ectopically delivering intracellular and extracellular mtHTT with or without inhibitors of secretion and glymphatic clearance to investigate the mechanism(S) of mtHTT release to CSF. Delineating the source and mechanism(s) of entry of CSF mtHTT protein will greatly enhance interpretation of this promising HD biomarker.

Disclosures: A.L. Southwell: None. **N.S. Caron:** None. **C. Yanick:** None. **Y. Xie:** None. **S.E. Smith:** None. **J. Song:** None. **I. Seong:** None. **B.R. Leavitt:** None. **M.R. Hayden:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.06/S9

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: Cedars-Sinai in support of CTSI grant UL1TR001881-01

Title: Human Huntington’s disease iPSC-derived corticalneurons display altered transcriptomics, morphology, and maturation

Authors: *V. B. MATTIS[1], S. R. MEHTA[2], C. TOM[2], Y. WANG[2], C. BRESEE[2], D. J. RUSHTON[3], P. P. MATHKAR[2], J. TANG[2]
[1]Board of Governors Regenerative Med. Inst., Cedars-Sinai, West Hollywood, CA; [3]Regenerative Med. Insitute, [2]Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Huntington's disease (HD) is a neurodegenerative disease caused by an expanded CAG repeat in the *Huntingtin* (*HTT*) gene. Induced pluripotent stem cell (iPSC) models of HD provide an opportunity to study the mechanisms underlying disease pathology in disease-relevant patient tissues. Murine studies have demonstrated that HTT is intricately involved in corticogenesis, and mutant (mt) HTT cannot compensate for the loss of wild-type HTT. However, the effect of mtHTT in human corticogenesis has not yet been thoroughly explored. This examination is critical, due to inherent differences in cortical development and timing between humans and mice. We therefore differentiated HD and non-diseased iPSCs into functional cortical neurons. While HD patient iPSCs can successfully differentiate towards a cortical fate in culture, the resulting neurons display altered transcriptomics, morphological and functional phenotypes indicative of altered corticogenesis in HD.

Disclosures: V.B. Mattis: None. **S.R. Mehta:** None. **C. Tom:** None. **Y. Wang:** None. **C. Bresee:** None. **D.J. Rushton:** None. **P.P. Mathkar:** None. **J. Tang:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.07/S10

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: MRC
HD CENTRE

Title: Huntington's disease phenotypes and disrupted corticostriatal connectivity observed in a novel human iPSC-derived *in vitro* co-culture model

Authors: *C. CASEY[1], Y. QUI[2], M. P. BENTHAM[2], E. SMITH[1], G. LIGNANI[2], S. SCHORGE[2], G. BATES[1], G. SCHIAVO[2], R. ANDRE[1], A. WOOD-KACZMAR[1], S. J. TABRIZI[1]
[1]Huntington's Dis. Res. Ctr., [2]Inst. of Neurol., Univ. Col. London, London, United Kingdom

Abstract: The corticostriatal (CS) pathway, comprising layer V cortical projection neurons (CPN) and medium spiny neurons (MSN), is one of the first brain pathways to succumb to Huntington's disease (HD) pathology. As a result, disrupted CS connectivity is evident and contributes to the motor and cognitive symptoms experienced by HD patients. Most studies to date elucidating the cellular drivers and mechanisms behind disrupted CS connectivity have originated from HD mouse models and human imaging data. There have been no investigations into the CS pathway using a purely human tissue-derived *in vitro* system. This project utilizes two iPSC lines derived from two closely related individuals; the control line, with 20/20 HTT CAG repeat lengths (20Q), and a juvenile HD line, with 20/73 CAG repeats (73Q). These lines

were differentiated in parallel to either MSNs or CPNs, and co-cultured in microfluidic chambers to physically recapitulate the human CS pathway.
The co-culture platform was constructed using either 20Q or 73Q iPSC-derived neurons, enabling comparisons between 'healthy' and 'diseased' pathways at a cellular level. Alternatively, crossed co-cultures, where 20Q CPNs synapse onto 73Q MSNs and vice versa, enabled the dissection of neuron-specific pathology and its impact on the CS pathway. High-resolution fluorescence microscopy has revealed the formation of CS synapses within MFC co-cultures, complimented by live cell imaging with calcium binding dye Fluo4, which demonstrates the successful transmission of calcium between neuronal populations within MFCs. Taken together, these data validate this platform as a reliable model of the CS pathway. Moreover, CPN cultures show an HD phenotype in their cytoskeletal dynamics, as axon projection efficiency is drastically reduced in 73Q CPNs compared to 20Q.
Furthermore, 73Q MSNs are more susceptible to BDNF-withdrawal induced cell death compared to 20Q cultures. Finally, the intrinsic membrane properties of iPSC-derived MSNs also differ with disease state, as 73Q MSNs are hyper-excitable, with an extended latency to fire and extended refractory period when compared to 20Q MSNs. These results provide a novel insight into the human CS pathway and suggest subtle differences in both the development and function of the CS pathway in HD.

Disclosures: C. Casey: None. **Y. Qui:** None. **M.P. Bentham:** None. **E. Smith:** None. **G. Lignani:** None. **S. Schorge:** None. **G. Bates:** None. **G. Schiavo:** None. **R. Andre:** None. **A. Wood-Kaczmar:** None. **S.J. Tabrizi:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.08/S11

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: MRC
HD Centre

Title: Investigating the role of the innate immune system in HD

Authors: *G. O'REGAN, R. ANDRE, J. POCOCK, S. J. TABRIZI
Univ. Col. London, London, United Kingdom

Abstract: Huntington's disease (HD) is a devastating neurodegenerative disease. It is caused by the presence of an expanded trinucleotide repeat in the *HTT* gene, resulting in expression of expanded polyglutamine-containing mutant HTT throughout the body. HD patients display a dysfunctional peripheral immune system up to sixteen years before disease onset. This is also

shown in HD animal models, where immune system dysfunction is found both in the periphery and CNS. This work aimed to assess the CNS component of the innate immune system, microglial cells, in a human HD model for the first time.
In order to achieve this, a unique cohort of iPSC lines from related individuals with varying expansion lengths (20Q, 56Q, 67Q, 73Q) were differentiated to microglia and subjected to a battery of functional tests, to assess the performance of HD microglia with increasing CAG lengths relative to controls.
Our results suggest that HD microglia display altered phenotypes compared to control microglia in a polyglutamine-length-dependent manner. Specifically, we found a hyper-reactive cytokine response profile upon stimulation with an immune challenge, increased production of ROS, elevated levels of phagocytosis upon stimulation, and reduced viability in the presence of an autophagy inhibitor.
This work represents this first assessment of HD microglia in a human HD model. We have shown that human HD microglia display the same dysfunction found in animal models of HD and in the peripheral immune cells of patients. Further research is now being conducted to characterise how these dysfunctional HD microglia may affect the health and function of neuronal cell types known to be affected in HD, to ascertain the impact of this dysfunction on disease pathology and progression.

Disclosures: G. O'Regan: None. **R. Andre:** None. **J. Pocock:** None. **S.J. Tabrizi:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.09/S12

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: FN Grant 31003A-165834/1

Title: Allele-specific gene editing for Huntington's disease mediated by a self-inactivating CRISPR/Cas9 system

Authors: *S. REGIO, G. VACHEY, M. REY, N. DEGLON
CHUV Pavillon 3, Lausanne, Switzerland

Abstract: Huntington’s disease (HD) is a fatal neurodegenerative disorder caused by CAG expansion in the *huntingtin* (*HTT*) gene. Considering that the mutation is a toxic gain-of-function, a promising approach would be to decrease the expression level of the mutant *HTT*. This can be achieved with genome-editing technologies, in particular the recently characterized CRISPR/Cas9 system. In a previous work, we described the kamiCas9, a self-inactivating CRISPR/Cas9 system designed for the transient expression of the Cas9 protein. We

demonstrated the high editing efficiency of WT and mutant HTT *in vitro* and *in vivo* with an important reduction of the off-target frequency. However, a selective editing of mutant HTT, using an allele-specific approach, represents the safest way to preserve WT HTT expression and functions. We thus developed more complex strategies to discriminate mutant and wild-type HTT genes by using single-guide RNA targeting sequences containing Single Nucleotide Polymorphism (SNP) in the HTT gene. A first *in vitro* screening, allow us to discriminate the two best candidates to trigger the cleavage of the mutant HTT respectively in the promoter and intron 1. Through this approach the exon 1 of the mutant *HTT*, which is the region containing the CAG expansion, could be selectively removed. This strategy has then been validated in human embryonic kidney 293T (HEK- 293T) cells and is currently tested in HD mouse models. These results demonstrate the potential of the self-inactivating CRISPR/Cas9 editing for applications in the context of neurodegenerative diseases and a proof of principle of allele-specific disruption of the human HTT gene.

Disclosures: S. Regio: None. **G. Vachey:** None. **M. Rey:** None. **N. Deglon:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.10/S13

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Cell type specific adenosine modulations in the mouse model of Huntington's disease

Authors: *Y. CHANG[1,2], C.-P. CHANG[1], H.-M. CHEN[1], Y. CHERN[1]
[1]Inst. of Biomed. Sciences, Academia Sinica, Taipei, Taiwan; [2]Taiwan Intl. Grad. Program in Interdisciplinary Neuroscience, Natl. Yang-Ming Univ. and Academia Sinica, Taipei, Taiwan

Abstract: Huntington’s disease (HD) is an autosomal dominant neurodegenerative disease caused by the expansion of CAG repeats in the exon 1 of *huntingtin* gene with no effective treatment. Adenosine is an important modulator in the brain. We have previously shown that the homeostasis and metabolism of adenosine are disrupted in HD. In addition, augmentation of adenosine in the brain caused protective effects on HD progression. Accumulated evidences suggest that different brain cells (including neurons, astrocytes and microglia) might contribute differently to the pathological regulation of adenosine in HD. We used an affinity- purified method to isolate mature neurons, astrocytes and microglia from the cortex of a HD mouse model (R6/2) at their presymptomatic and symptomatic stage (7 and 10.5 weeks old, respectively). The transcription levels of genes involved in adenosine homeostasis (including ecto-nucleotidases, adenosine deaminase, adenosine kinase and equilibrative nucleoside transporters) were examined. Our data showed that these adenosine homeostasis genes were distinctively regulated in different brain cells during HD progression. Further investigations

would provide important insights into understanding the dysregulation of adenosine homeostasis in HD and pave the way for the possible therapeutic intervention in the future.

Disclosures: Y. Chang: None. **C. Chang:** None. **H. Chen:** None. **Y. Chern:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.11/S14

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: FRQS postdoctoral fellowship

Title: The role and function of microglia in synaptic loss in Huntington's disease

Authors: *J. C. SAVAGE[1,2], M.-K. ST.-PIERRE[1,2], H. EL-HAJJ[1,2], M. G. SANCHEZ[1,2], F. CICCHETTI[1,2], M.-E. TREMBLAY[1,2]
[1]Axe Neurosciences, Ctr. De Recherche Du CHU De Quebec, Quebec, QC, Canada; [2]Univ. Laval, Quebec, QC, Canada

Abstract: Huntington’s disease (HD) is a dominantly inherited neurodegenerative disorder that affects cognitive and motor abilities by primarily targeting the striatum and cerebral cortex. HD is caused by a mutation elongating the CAG repeats within the *Huntingtin* gene, resulting in HTT protein misfolding. The severity and age of onset are correlated with the number of excess CAG repeats, with more repeats resulting in earlier disease onset. Although the genetic cause of HD has been established, the specific susceptibility of neurons within various brain structures has not been explained. Furthermore, there have been relatively few studies on the role of glial cells in HD, even though they express mutated HTT. We therefore set out to study the maturation and dysfunction of microglia, the brain’s resident macrophages, within the R6/2 model of HD. This transgenic model, which presents with 120+/-5 CAG, displays progressive motor deficits beginning at 6 weeks, with full incapacitation by 13 weeks. We studied microglial morphology, phagocytic capacity, and synaptic contacts and used focused ion beam-scanning electron microscopy (FIB-SEM) to reconstruct dendrites and count the number of synapses per micron in the striatum of R6/2 vs. wild-type littermates at various ages. At 3 weeks of age, prior to motor deficits or synaptic loss, microglia in R6/2 animals have a smaller morphological index, consistent with a mature ramified phenotype. By 10 weeks of age, microglia from R6/2 mice demonstrate increased phagocytosis, as revealed by light microscopy and immunoEM. Putative phagocytosis was confirmed using FIB-SEM in a subset of processes. Ultrastructural analysis indicated that microglial cell bodies from 3 or 10-week old R6/2 animals were more likely to perform extracellular degradation and contain phagocytic material than control. Furthermore, microglial processes in 10-week old R6/2 mice were less likely to make contact with synaptic

elements, while processes in 3-week old R6/2 mice were more likely to contact synapses. These preliminary findings indicate that microglia play an intimate role in HD pathogenesis and may be a target for therapeutic intervention.

Disclosures: J.C. Savage: None. **M. St.-Pierre:** None. **H. El-Hajj:** None. **M.G. Sanchez:** None. **F. Cicchetti:** None. **M. Tremblay:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.12/S15

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CIRM Bridges Trainee Funding
NINDS 1R01NS102486-01
NINDS R24 201603716
NIH NRSA Postdoctoral Fellowship F32NS090722
NIH NIGMS Predoctoral Fellowship T32GM099608
A Stewart's and Dake Family Gift
HELP4HD International

Title: Evaluation of effector domains fused to dCas9 to provide allele-specific silencing in Huntington's disease iPSC-derived neurons

Authors: *J. WALDO[1,2,3], P. DENG[2,3,4], J. A. HALMAI[2,3], J. L. CARTER[2,3], T. NGUYEN[1,2,3], S. DEL CAMPO[2,3,5], D. CAMERON[2,3], D. SEGAL[4], J. NOLTA[2], K. FINK[2,3]
[1]California State Univ. Sacramento, Sacramento, CA; [2]Stem Cell Program and Inst. for Regenerative Cures, [3]Dept. of Neurol., Univ. of California Davis Hlth. Systems, Sacramento, CA; [4]Genome Center, MIND Institute, and Biochem. and Mol. Med., Univ. of California, Davis, Davis, CA; [5]Humboldt State Univ., Humboldt, CA

Abstract: Huntington's disease (HD) is a fatal neurodegenerative disorder that affects approximately 1 in 10,000 people in the United States. HD is characterized by involuntary movements that often cause difficulty walking, talking, and swallowing. HD is inherited in an autosomal dominant manner and is caused by a CAG trinucleotide expansion in the first exon of the huntingtin gene (*HTT*). The CAG expansion in HD causes an abnormally long polyglutamine tract in the HTT protein that leads to protein misfolding, eventually resulting in neuronal cell death. CRISPR-dCas9 could provide a mechanism to specifically target and silence the mutant allele in HD. dCas9 lacks endonuclease activity while still retaining its DNA binding capabilities, allowing it to be used along with effector domains to modulate gene expression. Effector domains have an innate ability to modulate the heterochromatin structure and can be

fused to the dCas9 protein to decrease transcription of the target gene. Patient-derived stem cells that have naturally occurring disease-associated single nucleotide polymorphisms (SNPs) were used to validate mutant allele specific gRNAs.
In this study, the ability of dCas9 fused to different repressive domains to silence the mutant HTT allele in patient-derived neurons was assessed. HD patient-derived induced pluripotent stem cells (hiPSC) were differentiated into neuron-like cells in order to model the disease in a 2D culture system. The neuronal-like HD cells were evaluated using immunocytochemistry to confirm expression of MAP2 and Tuj1. Disease related phenotypes were assessed within patient derived neurons using a well-regarded published BDNF withdrawal assay. From the HD patient derived cells, SNPs within the regulatory regions of HTT were identified using SMRTseq. Allele-specific gRNAs were designed to target the identified disease-associated SNPs and delivered with a dCas9 fused to KRAB, Fog1, or DNMT3A in HD hiPSCs and the hiPSC-derived neurons . The ability of CRISPR-dCas9 to silence mutant HD allele was evaluated by KASP transcriptome analysis and Western Blotting to examine mutant HTT transcript and protein levels respectively. We hope this work will be a step toward developing a new therapeutic using the dCas9 system as a gene therapy for HD patients.

Disclosures: J. Waldo: None. **P. Deng:** None. **J.A. Halmai:** None. **J.L. Carter:** None. **T. Nguyen:** None. **S. Del Campo:** None. **D. Cameron:** None. **D. Segal:** None. **J. Nolta:** None. **K. Fink:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.13/S16

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI
Wellcome Trust 200181/Z/15/Z

Title: Compensation in neurodegenerative disease

Authors: *S. GREGORY, J. LONG[1], S. KLOPPEL[2], A. RAZI[3,4], E. SCHELLER[6], L. MINKOVA[6], E. JOHNSON[5], A. DURR[7], R. ROOS[8], B. R. LEAVITT[9], J. MILLS[1], J. C. STOUT[10], R. SCAHILL[5], S. TABRIZI[5], G. E. REES[11]
[1]Univ. of Iowa, Iowa City, IA; [2]Univ. Hosp. for Old Age Psychiatry, Bern, Switzerland; [3]NED Univ. of Engin. & Technol., Karachi, Pakistan; [5]Huntington's Dis. Ctr., [4]Univ. Col. London, London, United Kingdom; [6]Dept. of Psychiatry and Psychotherapy, Med. Center, Univ. of Freiburg, Freiburg, Germany; [7]Pitié-Salpêtrière Univ. Hosp., Paris, France; [8]Leiden Univ. Med. Ctr., Leiden, Netherlands; [9]Dept. of Med. Genet., Ctr. For Mol. Med. & Therapeut., Vancouver,

BC, Canada; [10]Monash Univ., Clayton, Australia; [11]Univ. Col. London, London, United Kingdom

Abstract: Compensation accounts for the dissociation between pathology and the absence of behavioural change during the premanifest and early stages of neurodegenerative disease. Despite neuronal loss, individuals with neurodegenerative disease function at a level similar to that of a healthy population until pathology overwhelms compensatory mechanisms and causes functional deterioration. The neural mechanisms underlying such compensation, however, are generally poorly understood due to the lack of an operational definition of compensation. Here, we describe both the first example of the modelling and empirical testing of compensation in neurodegenerative disease. Our operationalisation is based on both theoretical models of compensation in healthy ageing and Alzheimer's disease; and the hypothesis that compensation occurs where increased brain activation is required to maintain normal levels of behaviour until pathology becomes too severe. This compensatory relationship is characterized by non-linear longitudinal trajectories of brain activity and behavior with disease load increasing linearly over time across three sequential phases of disease progression. HD is an ideal model to test for such compensation as disease progression can be monitored many years prior to clinical diagnosis. We tested our model of compensation in a large cohort of premanifest and early HD gene-carriers from the TrackOn-HD study. Focusing on both cognitive and motor networks, brain activity was measured using task and resting-state fMRI, volumetric loss by structural MRI and behavior by task performance. Multivariate linear mixed models were fitted for each variable and trajectories tested. Maintained global cognition was associated with increased effective connectivity between the left and right dorsolateral prefrontal cortex, a central region in cognitive processing, while maintained motor performance was associated with increased connectivity between the left and right premotor cortex. Our empirical findings demonstrate theoretically-defined compensation in HD in networks central to the HD phenotype and can now be used to test both cross-sectional and longitudinal compensation in other neurodegenerative disease with similar patterns to HD.

Disclosures: J. Long: F. Consulting Fees (e.g., advisory boards); Dr. Long has a consulting agreement with NeuroPhage, is a paid consultant for Roche Pharma and Azevan Pharmaceuticals, and receives funding from CHDI, Michael J. Fox Foundation, and NIH.. **S. Kloppel:** None. **A. Razi:** None. **E. Scheller:** None. **L. Minkova:** None. **E. Johnson:** None. **A. Durr:** None. **R. Roos:** None. **B.R. Leavitt:** None. **J. Mills:** None. **J.C. Stout:** None. **R. Scahill:** None. **S. Tabrizi:** None. **G.E. Rees:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.14/S17

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI A3794
KBRI Grant 18-BR-01-03

Title: Cortical axon secretion of BDNF in the striatum is disrupted in a knock-in mouse model of Huntington's disease

Authors: *H. PARK[1,2]
[1]Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [2]Dept. of Mol. and Cell Biol., Univ. of California, Berkeley, CA

Abstract: Deficient BDNF signaling is known to be involved in neurodegenerative diseases such as Huntington's disease (HD). Mutant huntingtin (mhtt)-mediated disruption of either BDNF transcription or transport is thought to be a factor contributing to striatal atrophy in the HD brain. Whether and how activity-dependent BDNF secretion is affected by mhtt remains unclear. In the present study, we provide evidence for differential effects of mhtt on cortical BDNF secretion in the striatum during HD progression. By two-photon imaging of fluorescent BDNF sensor (BDNF-pHluorin and -EGFP) in acute striatal slices of HD knock-in model mice, we found deficient cortical BDNF secretion regardless the HD onset, but antisense oligonucleotide (ASO)-mediated reduction of htts only rescues BDNF secretion in the early HD brain before the disease onset. Although secretion modes of individual BDNF-containing vesicle were not altered in the pre-symptomatic brain, the full-fusion and partial-fusion modes of BDNF-containing vesicles were significantly altered after the onset of HD symptoms. Thus, besides abnormal BDNF transcription and transport, our results suggest that mhtt-mediated alteration in activity-dependent BDNF secretion at corticostriatal synapses also contributes to the development of HD.

Disclosures: H. Park: None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.15/S18

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant R01 NS098772 to N.B

Title: Mutant Huntingtin does not affect bioenergetics in human striatal neurons derived from inducible pluripotent stem cells of Huntington's disease patient

Authors: *J. HAMILTON[1], T. BRUSTOVETSKY[1], Y. PAN[2], A. SRIDHAR[2], J. MEYER[2,3], T. R. CUMMINS[2,3], N. BRUSTOVETSKY[1,3]

[1]Pharmacol. and Toxicology, Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Sch. of Sci., IUPUI, Indianapolis, IN; [3]Stark Neurosciences Res. Inst., Indianapolis, IN

Abstract: In early studies, mitochondrial dysfunction had been linked to Huntington's disease (HD) pathology. However, in recent years, a growing number of investigators reported the lack of overt detrimental effects of mutant huntingtin (mHtt) on mitochondria. In our previous studies with isolated brain mitochondria and cultured striatal neurons from YAC128 and R6/2 mouse models of HD, we demonstrated that mHtt does not deteriorate mitochondrial function or glycolytic activity (1-4). In the present study, we used human striatal neurons derived from inducible pluripotent stem cells from an unaffected individual and an HD patient with a HTT gene containing 72 CAG repeats. It is known that the induction of stemness and pluripotency resets the biological age of cells. Consequently, the newly generated neurons were considered young and pre-symptomatic. The human neurons were thoroughly characterized and were shown to express MAP2, DARPP32, GABA, and synapsin. In neurons derived from the HD patient, mHtt and wild-type huntingtin (Htt) were expressed in a 1:1 ratio. The sum of mHtt and Htt expression in cells from the HD patient was comparable to the level of Htt expression in cells from the unaffected individual. The human neurons were assessed for mitochondrial mass, mitochondrial membrane potential, mitochondrial ROS production, the levels of ADP and ATP, and for respiratory and glycolytic activity. All these parameters appeared to be similar in human neurons from the unaffected individual and the HD patient. On the other hand, in electrophysiological experiments, human neurons from the HD patient appeared to have a lower threshold for action potential generation compared with neurons from the unaffected individual. Thus, our results strongly argue against mitochondrial dysfunction as a factor in HD pathogenesis, in accordance with our earlier rodent studies, and suggest that mHtt may increase excitability of human striatal neurons.
1. Pellman, J.J., et al. (2015) *J. Neurochem.* 134, 652-667.
2. Hamilton, J., et al. (2015) *Hum. Mol. Gen.* 24, 4862-4878.
3. Hamilton, J., et al. (2016) *Hum. Mol. Gen.* 25, 2762-2775.
4. Hamilton, J., et al. (2017) *Neurochemistry International* 109, 24-33.

Disclosures: J. Hamilton: None. **T. Brustovetsky:** None. **Y. Pan:** None. **A. Sridhar:** None. **J. Meyer:** None. **T.R. Cummins:** None. **N. Brustovetsky:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.16/T1

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Huntington Society of Canada

Title: Early synaptic dysfunction in the hippocampus of Q175FDN Huntington's disease mice

Authors: A. S. RAVALIA, J. Y. LAU, J. G. QUIRION, *M. P. PARSONS
Biomed. Sci., Mem. Univ., St John's, NL, Canada

Abstract: Huntington Disease (HD) is an inherited neurodegenerative disease caused by a CAG repeat expansion in the gene encoding the huntingtin protein. The resultant polyglutamine-expanded mutant huntingtin (mHtt) protein triggers a myriad of synaptic disturbances. Interestingly, many of these synaptic defects can be detected prior to the onset of an overt behavioral phenotype, suggesting that presymptomatic therapeutic intervention may be required for maximal efficacy. The bulk of research on the early synaptic deficits in HD is conducted in the striatum, and while the striatum is the most vulnerable brain region in HD, HD is now recognized as a brain-wide disease and extrastriatal pathology contributes substantially to disease progression and severity. Relatively little is known regarding the early effect of mHtt on extrastriatal brain regions. Here, we studied various synaptic properties, including spine morphology, N-methyl-D-aspartate receptor (NMDAR) subcellular localization and downstream signaling, as well as activity-dependent synaptic plasticity in the hippocampus of Q175FDN heterozygous HD mice. All experiments were performed at 3 months of age, prior to the emergence of an HD-like behavioral phenotype in this model, and we focused on the hippocampus due to its undisputed involvement in cognitive function and the debilitating cognitive symptoms described by many HD patients. We found a dramatic shift in the spine maturity profile in the CA1 region of the Q175FDN hippocampus, with Q175FDN mice having significantly more immature spines (thin) and significantly less mature (mushroom) spines in comparison to wild-type littermates. Multi-electrode array recordings of synaptic connectivity reveled subtle impairments in activity-dependent synaptic plasticity, and we also observed clear NMDAR mislocalization and enhanced caspase-3 signaling downstream of NMDAR activation in the Q175FDN hippocampus. In all, our data demonstrate clear detrimental effects of mHtt expression on hippocampal function in presymptomatic HD. The identified synaptic deficits are likely to contribute, at least in part, to the emergence of debilitating cognitive symptoms associated with HD.

Disclosures: A.S. Ravalia: None. **J.Y. Lau:** None. **J.G. Quirion:** None. **M.P. Parsons:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.17/T2

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CIHR Grant FDN-143210
Teva Pharmaceutical Industries, Ltd

Title: Rescue of homeostatic plasticity in YAC128 cortical neurons by pridopidine through modulation of Sigma1R and BDNF signaling

Authors: *A. I. SMITH-DIJAK[1], W. NASSRALLAH[1], L. ZHANG[1], M. GEVA[2], M. R. HAYDEN[2], L. A. RAYMOND[1]
[1]Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada; [2]Teva Pharmaceut. Industries, Ltd, Even Yehuda, Israel

Abstract: Homeostatic plasticity is a key mechanism for maintaining stability in neural circuits throughout the brain. Even as individual synapses undergo long-term potentiation or depression, homeostatic synaptic scaling preserves the relative weighting of synaptic strength and numbers locally, while adjusting the overall magnitude of synaptic input to maintain the neuronal firing rate in a physiological range. This is thought to be important for maintaining capacity for new learning and mental flexibility - cognitive functions that are impaired early in Huntington disease (HD). Previous work in rodent cortical neurons has shown that blockade of action potentials for 24-48h by treatment with tetrodotoxin (TTX) results in up-scaling of excitatory glutamatergic synapses, mediated by reduced activity-dependent release of Brain-Derived Neurotrophic Factor (BDNF). Since the mutant huntingtin protein reduces BDNF transcription and transport in cortical neurons, we hypothesized that cortical neurons from the YAC128 HD mouse model would already have a deficit in BDNF signaling and therefore reduced capacity to respond to TTX with synaptic up-scaling. In addition, we postulated that pridopidine, suggested to stabilize total functional capacity (TFC) in a recent clinical trial (PRIDE-HD) and also shown to upregulate BDNF signaling in rodents (Geva M et al., Hum Mol Genet 25:3975, 2016), could rescue a deficit in homeostatic plasticity in YAC128 cortical neurons. To test this, we made electrophysiological recordings from YAC128 and wild-type mouse cortical neuronal cultures to measure function of excitatory glutamatergic synapses in control conditions vs. after 48h exposure to TTX. Wild-type cortical neurons responded to action potential silencing by increasing the frequency and amplitude of miniature excitatory synaptic currents (mEPSCs; which reflect the strength of synapses onto a neuron), whereas there was no response for either measure in YAC128 cortical neurons. In contrast, pre-treatment with pridopidine restored synaptic up-scaling in YAC128 neurons after a subsequent 48h exposure to TTX. We will also present data regarding the role of BDNF in the synaptic scaling which we observed and its rescue by pridopidine. In addition, we will present evidence for the involvement of the sigma-1 receptor, which has been hypothesized to be the primary site of action of pridopidine in its treatment of HD, in this rescue. Our results shed new light on mechanisms by which pridopidine may slow the progressive decline in functional capacity in HD, and suggest a role for this drug in ameliorating cognitive deficits associated with the prodromal and early stages of disease.

Disclosures: W. Nassrallah: None. **L. Zhang:** 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.; Teva Pharmaceutical Industries, Ltd. **M. Geva:** A. Employment/Salary (full or part-time):; Teva Pharmaceutical Industries, Ltd. **M.R. Hayden:** A. Employment/Salary (full or part-time):; Teva Pharmaceutical Industries, Ltd. **L.A. Raymond:** 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.; Teva Pharmaceutical Industries, Ltd. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Teva Pharmaceutical Industries, Ltd.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.18/T3

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Characterization of neurodevelopmental delays in iPSC-derivede striatal cultures from patients with Huntington's disease

Authors: *P. P. MATHKAR, D. SURESH, J. DUNN, V. B. MATTIS
BOG Regenerative Med. Institute, Cedars Sinai, Beverly Hills, CA

Abstract: Abstract: Huntington’s Disease (HD) is a fatal neurodegenerative disorder characterized by progressive neural atrophy, causing the atrophy and loss of the majority of neurons within the striatum in particular. HD is caused by CAG repeat expansion in *Huntingtin* (*HTT*) gene. Previous studies using human induced pluripotent stem cells (hiPSCs), or somatic cells reprogrammed to a pluripotent state, from HD patients have demonstrated a delayed developmental phenotype upon differentiation towards a striatal fate, including increased expression of nestin during the differentiation process, a type VI intermediate filament specific to neural progenitor cells. It was therefore hypothesized that a delayed striatal maturation in HD results in development abnormalities which adversely affects the neuronal homeostasis leading to the downstream degeneration of striatal neurons. This study was designed to further characterize a HD model using human iPSC to further characterize the decrease in neuronal/glial maturation caused by the expanded HTT repeats, and to elucidate the mechanism of such delayed maturation. 5 HD and 4 control lines were hence differentiated towards striatal fate and characterized for the expression of adult and progenitor neuronal and glial markers at different time points. Additionally, we investigated if the similar phenotype is recapitulated *in vivo* using an HD mouse model. In conclusion, this study challenges the traditional notion of HD as an adult onset neurodegenerative disorder by possibly implicating alterations in neurodevelopment.

Disclosures: P.P. Mathkar: None. **D. Suresh:** None. **J. Dunn:** None. **V.B. Mattis:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.19/T4

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Characterizing neurodevelopmental deficits in corticogenesis in Huntington's disease using 3D organoid models

Authors: *S. MEHTA, V. MATTIS, P. MATHKAR
Cedars-Sinai, Los Angeles, CA

Abstract: Huntington disease (HD), is a dominantly inherited disorder caused by a CAG expansion mutation in the huntingtin (HTT) gene. The adult form of HD exhibits a late onset of symptoms, nonetheless, there is also a long pre-symptomatic stage which has been increasingly studied and acknowledged as important for disease development. Furthermore, children at a higher risk of HD exhibit symptoms like a smaller head size or lower BMI, which suggest neurodevelopmental deficits. Evidence from recent stem cell studies supports the idea that mutant HTT-dependent changes may be detected early, such as impaired neural rosette formation or increased susceptibility to growth factor withdrawal, even at the naïve pluripotent cell stage. Therefore, it is important to elucidate the pathogenesis of HD along its differentiation pathway in order to identify the early processes relevant to developmental defects and disease onset. Data from iPSC derived 2D HD cultures as well as brain region specific abnormalities found in in vivo murine and human samples suggests that artificial culture systems may be inefficient in studying the complete effect of mutant HTT or identifying therapeutic targets. 3D organoid culture systems may have the potential to recapitulate conditions more similar to in vivo, thereby providing a more viable model to study disease onset and progression. This innovative approach will use patient cells to examine and highlight key HD-specific differences in corticogenesis, which will elucidate novel disease mechanisms for therapeutic intervention targeting.

Disclosures: S. Mehta: None. **V. Mattis:** None. **P. Mathkar:** None.

Poster

657. Huntington's Disease: Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 657.20/T5

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI Foundation
Wellcome Trust grant 200181/Z/15/Z

Title: Modelling the trajectory of cortical atrophy in Huntington's disease

Authors: *E. JOHNSON[1], G. ZIEGLER[2], W. PENNY[3], G. E. REES[1], S. J. TABRIZI[1], R. I. SCAHILL[1], S. GREGORY[1]
[1]Univ. Col. London, London, United Kingdom; [2]German Ctr. for Neurodegenerative Dis., Bonn, Germany; [3]Sch. of Psychology, Univ. of East Anglia, Norwich, United Kingdom

Abstract: Huntington's disease (HD) is a neurodegenerative disease typically characterised by early striatal atrophy extending to the cortex as the disease progresses. Despite histological evidence of widespread grey matter atrophy by end-stage-disease, the progression of cortical atrophy in HD has yet to be fully characterised. Here, we have used a novel approach to map cortical atrophy during the transition from premanifest to motor clinical diagnosis of manifest HD, modelling both non-linear and linear atrophy in a large cohort of participants, with MRI data spanning 6 years before and 5 years after clinical diagnosis.
Structural MR images from 49 HD gene-carrier participants were included in the analysis, collected as part of the longitudinal, multi-site TRACK-HD and TrackOn-HD studies. Participants underwent yearly 3T MRI scans, with up to 7 visits, along with clinical examination and cognitive testing. Participants were classified as premanifest at recruitment with subsequent diagnosis as manifest HD occurring at a later time-point during the study. Each set of images for each participant underwent longitudinal registration and were segmented using MALP-EM, with cortical and subcortical volumes calculated. A hierarchical dynamical model was applied at the individual (first-) level to map individual trajectories. A group (second-) level model was then used to estimate group-wise change, accounting for the effects of covariates. This approach was used to measure gross atrophy, linear rate of atrophy and non-linear accelerations in atrophy.
Over the time period examined, atrophy was highest in frontal and motor regions, particularly the supplementary motor cortex (11.66% per decade) with greatest linear rates of atrophy in the frontal cortex and greatest acceleration of atrophy in the motor cortex at the point of clinical motor diagnosis.
This study provides the most complete characterisation of cortical atrophy in HD presented to-date. The results suggest that the degree of atrophy occurring in the cortex around time of HD diagnosis is much higher than previously reported, and a number of regions show accelerations in atrophy around motor diagnosis. These findings have important implications for the understanding and treatment of HD and other neurodegenerative conditions.

Disclosures: E. Johnson: None. **G. Ziegler:** None. **W. Penny:** None. **G.E. Rees:** None. **S.J. Tabrizi:** None. **R.I. Scahill:** None. **S. Gregory:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.01/T6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: FDA Protocol #7579.01

Title: Microglia responses to lipopolysaccharide are likely primarily directed towards vasculature and are exacerbated by pronounced and prolonged hypothermia at high doses

Authors: *J. F. BOWYER[1], K. M. TRANTER[1], S. M. LANTZ[1], S. SARKAR[1], J. P. HANIG[2], J. N. HESS[1]
[1]Neurotoxicology, Natl. Ctr. for Toxicological Res. Div. of Neurotoxicology, Jefferson, AR; [2]Ctr. for Drug Evaluation and Research/ FDA, Silver Spring, MD

Abstract: For the past two years, we have been conducting histological studies to determine how microglia in adult female BALBc mice respond to systemic administration of lipopolysaccharide (LPS), one of the original compounds shown to evoke neuroinflammation in the brain. Antibodies to allograft inflammatory factor (Aif1, a.k.a. Iba1) and integrin alpha (Itgam, a.k.a. Cd11b) were used to track morphological changes in microglia. Platelet/endothelial cell adhesion molecule 1 (Pecam1, a.k.a. Cd31) was used to visualize vasculature in the forebrain. Doses of 1, 2 and 3 mg/kg LPS were administered either subcutaneously (s.c.) or intraperitoneally (i.p.) and the resulting neurotoxicity was evaluated at 6 h to 2 weeks later. LPS did not cause neurodegeneration at 1 mg/kg (s.c. or i.p.) and 2 mg/ kg s.c. Also, 2 mg/kg LPS i.p., did not cause neurodegeneration in most cases. Neuroinflammation/activation was determined by increased size of Iba1 immunoreactive microglia and their increased close association with Cd31 immunoreactive vasculature. Microglial activation, with minimal or no increase in number, was detectable within 12 h after LPS and pronounced within 24 h, with the effect waning after 3 days. Activation in the hippocampus and somatosensory cortex was most pronounced while activation in the thalamus was less. Within 24 h, almost all of the microglia soma in the hippocampus and cortex were closely associated with vasculature, not neurons, and had increased more than 2-fold in size. Macrophages entered the vasculature and vascular morphology was adversely affected in the few cases where the higher doses of LPS (≥2 mg/ kg i.p. or 3 mg/kg s.c.) produced prolonged hypothermia. It is not clear whether neurodegeneration would have eventually occurred in these mice. Prolonged hypothermia has been shown by other investigators to cause blood-brain barrier leakage, and this may be the reason for the increased vascular toxicity at the higher doses. We hypothesize that immune signals (possibly Ccl2, Ccl7 and Ccl20) from vascular endothelium adversely affected by LPS are triggering the aggregation of the microglia around vasculature.

Disclosures: J.F. Bowyer: None. **K.M. Tranter:** None. **S.M. Lantz:** None. **S. Sarkar:** None. **J.P. Hanig:** None. **J.N. Hess:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.02/T7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

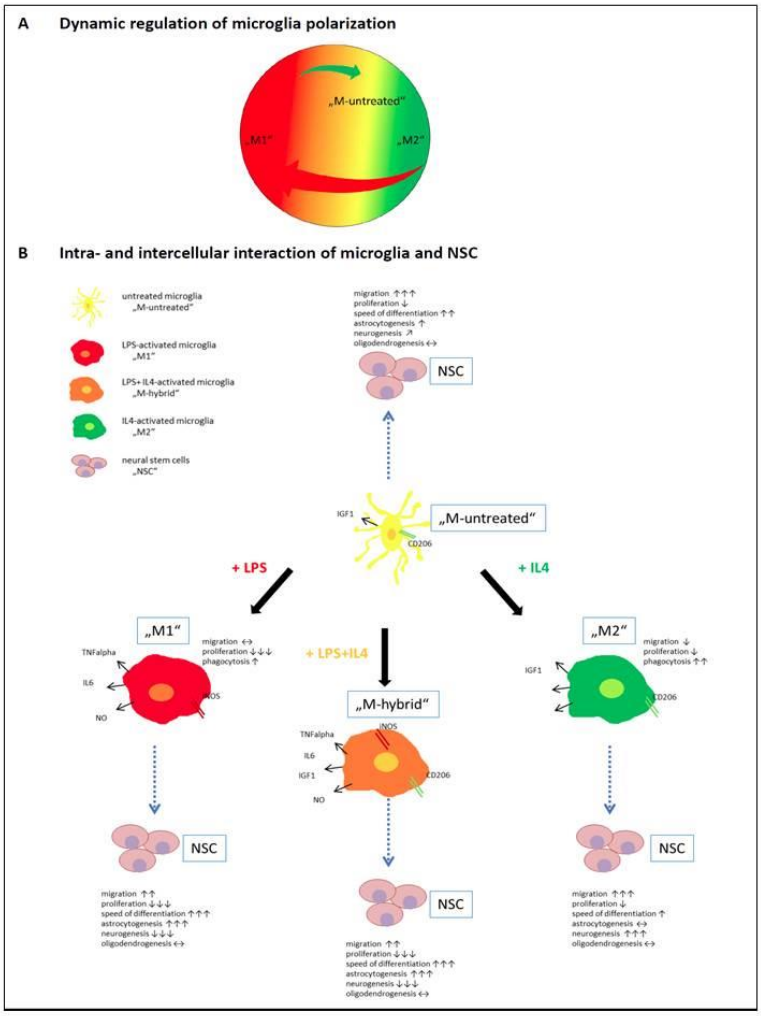
Support: Marga-und-Walter-Boll-Foundation (#210-10-15)
Koeln Fortune Program / Faculty of Medicine, University of Cologne, Germany (339/2015)

Title: The “colour-wheel” of activated primary microglia and their multifaceted effects on endogenous neural stem cells *in vitro*

Authors: *M. SCHROETER[1], S. U. VAY[2], L. J. FLITSCH[2], M. RABENSTEIN[2], R. ROGALL[2], S. BLASCHKE[3], G. R. FINK[5], M. A. RUEGER[4]
[1]Dept. of Neurology, Univ. Hosp. Cologne, Cologne, Germany; [2]Dept of Neurol., [3]Dept. of Neurol., Univ. of Cologne, Koeln, Germany; [4]Univ. of Cologne, Cologne, Germany; [5]Res. Ctr. Jülich, Jülich, Germany

Abstract: Microglia - the resident immune cells of the brain - are activated after lesions to the brain such as cerebral ischemia and polarize towards a classic “M1” pro-inflammatory or an alternative “M2” anti-inflammatory phenotype following characteristic temporo-spatial patterns, contributing either to secondary tissue damage or to regenerative responses. They closely interact with endogenous neural stems cells (NSC) residing in distinct niches of the adult brain. The current study aimed at elucidating the dynamics of microglia polarization and their differential effects on NSC function. Primary rat microglia *in vitro* were polarized towards an M1 phenotype by LPS, or to an M2 phenotype by IL4, while simultaneous exposure to LPS plus IL4 resulted in a hybrid phenotype expressing both M1- and M2-characteristic markers. M2 microglia migrated less but was more phagocytically active than M1 microglia. Defined mediators switched microglia from one polarization state to the other, a process more effective when transforming M2 microglia towards M1 than vice-versa. Polarized microglia had differential effects on the differentiation potential of NSC *in vitro* and *in vivo*, with M1 microglia promoting the generation of astrocytes, while M2 microglia supported neurogenesis. Regardless of their polarization, microglia inhibited NSC proliferation, increased NSC migration, and accelerated NSC differentiation upon mitogen withdrawal. Overall, this study unravels the complex conditions

governing microglia polarization, and the effects of differentially polarized microglia on key functions of NSC. Data will facilitate the prospective development of innovative therapeutic concepts supporting the regenerative capacity of the brain, e.g. after cerebral ischemia



Disclosures: **M. Schroeter:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); MS receved honoraria (speaker's bureaus) from Alexion, Bayer, Baxalta/Shire, Biogen, CSL Behring, Genzyme, Grifols, Merck, Miltenyi Biotec, Novartis, Roche, Teva. **S.U. Vay:** None. **L.J. Flitsch:** None. **M. Rabenstein:** None. **R. Rogall:** None. **S. Blaschke:** None. **G.R. Fink:** None. **M.A. Rueger:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.03/T8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Investigations on improving the culturing conditions to retain the *in vivo*-like phenotype of primary microglia

Authors: *S. BARENDRECHT, R. EICHENTOPF, B. HIETEL, S. SCHILLING, H. CYNIS
Fraunhofer IZI-MWT, Halle (Saale), Germany

Abstract: Microglia are the phagocytic immune cells in the CNS, and make up 8-13% of the total cell population in the brain. Microglia cells derive from early yolk-sac macrophages and have many different functions, both in normal brain development and in pathological conditions. Besides their phagocytic function, microglia cells are known to secrete cytokines in response to certain stimuli. Overproduction of these cytokines in disease conditions, however, could lead to neuron loss and thereby aggravate pathology. The exact role of microglia in brain disorders remains elusive, because *in vitro* studies with isolated cells are hampered by a rapid loss of the *in vivo* microglial phenotype. We hypothesize that this loss of expression of microglia specific genes in culture is due to a lack of input from other CNS cells.
The aim of our study is to culture primary microglia *in vitro* in which the *in vivo* phenotype is retained or restored. We are comparing different isolation methods and culturing conditions for primary microglia. The culturing conditions are based on factors normally present in the CNS and known to be important for the activation state of microglia. To test the preservation of an *in vivo* phenotype, we analyze gene expression using qRT-PCR and gene arrays, as well as functional assays.
Compared to regular culturing, the culturing conditions for primary microglia from newborn mice tested in our lab significantly increased the expression of 5 out of 7 genes, previously found to be specific for microglia. Although an increase of microglia specific gene expression was accomplished, the gene expression was significantly lower in primary microglia from newborn mice than in freshly isolated microglia from adult mice. Functionally, we found no effect of the different culturing conditions using a phagocytosis assay.
Our culture conditions are able to at least partially mimic the environment in the CNS, and thereby improve the phenotype of primary microglia from newborn mice *in vitro*. Our next step is to isolate primary microglia from adult brains and use our established culturing conditions to prevent the loss of the *in vivo* microglial phenotype in these cells. We will compare these microglia cells to freshly isolated microglia in both gene expression and functionality.

Disclosures: S. Barendrecht: None. **R. Eichentopf:** None. **B. Hietel:** None. **S. Schilling:** None. **H. Cynis:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.04/T9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Stanley Medical Research Grant

Title: Development of a cox-2 pet tracer as an activated microglia-specific biomarkers in cns disorders

Authors: *F. F. WAGNER[1], M. WEIWER[1], M. RILEY[3], M. PLACZEK[3], D. WILTON[4], M. MELANSON[2], A. CAMPBELL[1], J. SACHER[1], B. BAJRAMI[2], A. FAYET[1], C. ROMANO[1], J. GALE[2], Y.-L. ZHANG[1], J. COTTRELL[1], B. A. STEVENS[4], J. HOOKER[3]
[1]Stanley Ctr. for Psychiatric Res., [2]Broad Inst., Cambridge, MA; [3]MGH, Charlestown, MA; [4]Harvard Med. Sch. Neurobio., Boston Children's Hosp., Boston, MA

Abstract: Dysregulated microglia-dependent synaptic pruning through the complement cascade and associated neuroinflammation processes have been linked with a wide range of neurodevelopment and neurodegenerative diseases such as schizophrenia, Alzheimer and Huntington disorders. Here we investigate the possibility of using cox-2, the rate-limiting enzyme in the biosynthesis of prostaglandins during the inflammation process, as a clinical marker of pathophysiological onset and progression of Huntington’s disease through the development of a brain-penetrant cox-2 specific PET radiotracer.

Disclosures: F.F. Wagner: None. **M. Weiwer:** None. **M. Riley:** None. **M. Placzek:** None. **D. Wilton:** None. **M. Melanson:** None. **A. Campbell:** None. **J. Sacher:** None. **B. Bajrami:** None. **A. Fayet:** None. **C. Romano:** None. **J. Gale:** None. **Y. Zhang:** None. **J. Cottrell:** None. **B.A. Stevens:** None. **J. Hooker:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.05/T10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: FWF; DK MOLIN-W1241

Title: Lysophosphatidic acid (LPA) promotes a pro inflammatory response in microglia cells via the JNK signaling pathway

Authors: *J. PLASTIRA, E. BERNHART, M. GOERITZER, C. KOYANI, W. SATTLER
Med. Univ. of Graz, Mol. Biol. and Biochem., Graz, Austria

Abstract: Microglia are the resident immune cells of the brain and are able to detect subtle alterations of the finely tuned micromilieu in the CNS. They regulate multiple aspects of inflammation, such as repair, regeneration, toxicity, and immunosuppression depending on their different activation states. Extrinsic signals, depending on disease context, determine whether microglia acquire a beneficial or detrimental phenotype. Their crucial role in brain homeostasis makes these cells potential therapeutic targets, which necessitate a thorough understanding of polarization cascades, transcriptome profiles, and pathways that modulate their function.
Lysophosphatidic acid (LPA) is produced via the autotaxin pathway or by phospholipase A-mediated pathways. LPA has numerous biological functions mediated by downstream signaling through different receptors. Aberrant LPA signaling has been implicated in several neurological disorders including neuropathic pain, traumatic brain injury, and schizophrenia. We have already unraveled a new role for LPAR5 via which LPA potently regulate microglia function and induce an inflammatory response. The distinct signaling cascades and transcriptional programs that drive this LPA-mediated M1-like signature in microglia are currently unknown.
Using an LPA ELISA we observed significally elevated LPA levels in CSF from AD patients and in both CSF and brain tissue of 5xFAD mice. In a mouse model of endotoxemia, increased LPA levels were detected in the cortices of LPS treated mice compared to controls.
Regarding the possible downstream pathways that controls the LPA induced microglial pro inflammatory response; immunoblotting results revealed that inhibition of JNK abrogates the activation of transcription factors (STAT1, p65 NFκB, and cJun) mainly responsible for the promotion of a pro inflammatory phenotype. Flow cytometry and immunofluorescence analysis showed that LPA induced expression of M1 markers is JNK dependent. In addition, we observed that the JNK pathway controls the LPA induced secretion of pro inflammatory cytokines and chemokines (IL-1β, TNFα, IL-6, CCL5, CXCL2, and CXCL10). These findings were accompanied by limited ROS and NO production, and decreased microglial cytotoxicity following inhibition of JNK pathway.
A better understanding of the role of bioactive lipids in microglia pathophysiology and the characterization of signaling cascades that control these responses can open new directions in modulating microglia function. Unraveling the LPA/LPAR-induced downstream kinase networks will support the development of targeted therapies to interfere with microglia polarization states.

Disclosures: J. Plastira: None. **E. Bernhart:** None. **M. Goeritzer:** None. **C. Koyani:** None. **W. Sattler:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.06/T11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: AG043788
AG038910
NS100294
NIRG-10-174150

Title: The voltage-gated potassium channel Kv1.3 is required for microglial pro-inflammatory activation *in vivo*

Authors: *J. DI LUCENTE[1], H. M. NGUYEN[2], H. WULFF[2], L.-W. JIN[1], I. MAEZAWA[1]
[1]Pathology and laboratory medicine, UC Davis, Sacramento, CA; [2]Pharmacol., UC Davis, Davis, CA

Abstract: Microglia show a rich repertoire of activation patterns regulated by a complex ensemble of surface ion channels, receptors, and transporters. We and others have investigated whether microglia vary their K^+ channel expression as a means to achieve functional diversity. However, most of the prior studies were conducted using *in vitro* models such as BV2 cells, primary microglia, or brain slices in culture, which may not accurately reflect microglia physiology in adult individuals. Here we employed an *in vivo* mouse model of selective innate immune activation by intracerebroventricular injection of lipopolysaccharides (ICV-LPS) to determine the role of the voltage-gated Kv1.3 channel in LPS-induced M1-like microglial activation. Using microglia acutely isolated from adult brains, we detected Kv1.3 and Kir2.1 currents, and found that ICV-LPS increased the current density and RNA expression of Kv1.3 but did not affect those of Kir2.1. Genetic knockout of Kv1.3 abolished LPS-induced microglial activation exemplified by CD11b immunoreactivity and expression of pro-inflammatory mediators such as IL-1β, TNF-α, IL-6 and iNOS. Moreover, Kv1.3 knockout mitigated the LPS-induced impairment of hippocampal long-term potentiation (hLTP), suggesting that Kv1.3 activity regulates pro-inflammatory microglial neurotoxicity. Pharmacological intervention using PAP-1, a small molecule that selectively blocks homotetrameric Kv1.3 channels, achieved anti-inflammatory and hLTP-recovery effects similar to Kv1.3 knockout. We conclude that Kv1.3 is required for microglial M1-like pro-inflammatory activation *in vivo*. A significant implication of our *in vivo* data is that selective Kv1.3 blockers could be therapeutic candidates for neurological diseases where microglia-mediated neurotoxicity is implicated in the pathogenesis.

Disclosures: J. Di Lucente: None. **H.M. Nguyen:** None. **H. Wulff:** None. **L. Jin:** None. **I. Maezawa:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.07/T12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Research Grant from AMED, Japan
Research Grant from MEXT, Japan (17K08330)

Title: Microglia is not the resource but the modulator of the cytokines/chemokines in inflammatory neurovascular unit

Authors: *K. SATO[1], K. HOSHIKAWA[1], Y. KANDA[2], Y. SHIGEMOTO-MOGAMI[1]
[1]Lab. Neuropharmacol, Div. Pharmacol, [2]Div. Pharmacol, Natl. Inst. Hlth. Sci., Kanagawa, Japan

Abstract: Neuroinflammation is associated with blood brain barrier (BBB) disruption in the CNS diseases. Although microglial activation and subsequent concentration changes in various kinds of cytokines/chemokines (C/Cs) are suggested to be key steps to worsen the neuroinflammation and BBB disruption, little data are available concerning the significance of the interaction of microglia with BBB cells in this process. In this study, we mimicked neuroinflammation by adding LPS-activated microglia (LPS-MG) to the abluminal side of in vitro BBB model comprised of endotherial cells (EC), pericytes (Peri) and astrocytes (Ast). We then measured the abluminal concentrations of 27 kinds of C/Cs. We also investigated the contribution of interactions between LPS-MG and BBB cells to their concentration changes. LPS-MG induced BBB collapse as revealed by the decrease in the trans-endothelial electrical resistance (TEER) and in the expression levels of tight junction proteins (TJs). In this condition, 19 C/Cs were remarkably increased in the abluminal side. LPS-MG alone released 10/19 C/Cs, but unexpectedly, their concentrations were even lower than those detected in the in vitro BBB model supplemented with LPS-MG. On the contrary, co-culture of LPS-MG with Ast caused remarkable increases in 12/19 C/Cs, while co-culture with vascular cells (EC and Peri) caused significant increase in 1/19 C/C (fractalkine). These results suggest that C/C dynamics in neuroinflammation associated with BBB breakdown is mainly attributed to the interaction of activated microglia with Ast.

Disclosures: K. Sato: None. **K. Hoshikawa:** None. **Y. Kanda:** None. **Y. Shigemoto-Mogami:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.08/T13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 5R01MH109165-03

Title: Microglia gain functional IL-1R1 following chronic peripheral inflammation

Authors: *D. NEMETH[1], X. LIU[2], D. J. DISABATO[3], C. NEGRAY[4], N. QUAN[5]
[1]Inst. For Behavioral Med. Res., Columbus, OH; [3]Neurosci., [4]Col. of Dent., [2]The Ohio State Univ., Columbus, OH; [5]Dept Biosci., Ohio State Univ., Columbus, OH

Abstract: Peripheral inflammation is known to sensitize the central nervous system (CNS) and has been associated with the exacerbation of neurodegenerative disorders, such as prion diseases. The mechanism by which peripheral inflammation can sensitize and amplify CNS inflammation is unknown. To mimic chronic peripheral inflammation, intraperitoneal injections of lipopolysaccharide (LPS) were administered for four consecutive days (4d LPS). 4d LPS elicits microglial activation, as seen by an increase in percent Iba-1 area, whereas a single LPS injection does not. Microglia were observed to wrap around blood vessels in the cortex after 4d LPS, yet this action is attenuated in mice deficient in Interleukin-1 Receptor 1 (IL-1R1), suggesting IL1R1 is an important receptor in mediating microglial migration. Using a genetic mouse model, in which IL-1R1 is specifically restored in microglia (CX3CR1Cre IL-1R1$^{r/r}$); we were able to detect IL-1R1 mRNA expression after 4d LPS but not in PBS injected controls. Intracerebroventricular injection of IL-1β in LPS primed CX3CR1Cre IL-1R1$^{r/r}$ animals exhibited microglial morphological changes and an increase in IL-1R1 and IL-1β mRNA compared to PBS injected controls, indicating a gain of function on microglia. Overall, these data suggest a potential mechanism by which peripheral inflammation can sensitize the CNS microglia and contribute to augmenting neurodegenerative diseases.

Disclosures: D. Nemeth: None. **X. Liu:** None. **D.J. Disabato:** None. **C. Negray:** None. **N. Quan:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.09/T14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: FONDECYT 1171645
FONDECYT 1171434
3180553

Title: Effect of *in vivo* activation of Fas-mediated apoptosis cascade by AP20187 on microglia in MaFIA mice

Authors: *S. BELTRAN-CASTILLO[1], J. EUGENIN[2], R. VON BERNHARDI[1]
[1]Neurología, Pontificia Univ. Católica De Chile, Santiago, Chile; [2]Univ. de Santiago, USACH, Santiago, Chile

Abstract: Microglia are the main innate immune effector cells of the brain and the main generator of inflammatory cytokines and oxidative products in the CNS. Beyond the immunological role, new and controversial functions have been described for microglia in normal and pathologic functions. To elucidate the role of microglia in those new functions, animal models that allow us to eliminate the microglia from CNS in vivo, without affecting the innate immune system of the whole animal, are especially important. A possibility is the use of the macrophage Fas-induced apoptosis (MaFIA) transgenic mice. In this model, a murine c-fms promoter induces the expression of a transgene containing a suicide fusion protein made of the FK506-binding protein and the cytoplasmic domain of Fas and enhanced green fluorescent protein (EGFP) only in macrophages and microglia. Because the dimerization of suicide protein and the induction of Fas-mediated apoptosis requires the administration of AP20187, a homodimerizer drug with limited ability to cross the blood-brain barrier, we injected AP20187 into the cerebral ventricles. Through stereotaxia and under deep isofluorane anesthesia, we implanted a 3.0 mm dummy cannula contained into a 2.5 mm guide cannula at lateral ventricle (-0.3 mm A.P., 1 mm M.L. axes) in 3-6 m old MaFiA mice. After 4 days (d) of recovery, the dummy cannula was replaced for a 3.0 mm internal cannula connected to a 5 µL Hamilton syringe for delivery of a) 0.2 µL of saline, or 100 ng Kg^{-1} AP20187 every 24 h per 5 d, b) 1 µg Kg^{-1} every 12 or 24 h per 5 or 8 d or c) simultaneous i.p. and i.v. injection of 5 µg Kg^{-1} every 24 h per 5 d. The number and morphology of microglia after treatment were evaluated by IBA1 immunostaining in 40 µm sections of hippocampus and brainstem. The inflammatory status was evaluated by ELISA. Whereas 100 ng Kg^{-1} or 1 µg Kg^{-1} AP20187 every 24 h per 5 or 8 d, did not modify microglia number in the hippocampus and brainstem, treatment with 1 µg Kg^{-1} AP20187 every 12 h per 5 d induced a 15% decrease on microglia number and conspicuous

morphological changes. Morphological changes consisted in an increased amoeboid activated state with reduction in both length and number of branches. The maximal effect on microglia was observed when mice received the simultaneous application of i.v. and i.p. AP20187, reaching a 28% reduction of microglia in brainstem areas. We suggest that, due to the fast proliferation of microglia that allows its rapid repopulation on the CNS, it is required chronic high levels of AP20187 for a most effective microglia ablation. MaFIA mice can be used as a complementary method for evaluating the role of microglia in conditions like neurodegenerative disorders.

Disclosures: S. Beltran-Castillo: None. **J. Eugenin:** None. **R. von Bernhardi:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.10/T15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CIHR
ALS Canada

Title: Dissociation of mRNA and protein molecular signatures in activated microglia

Authors: *J. KRIZ[1], H. BOUTEJ, G1J 2G3[2], L.-C. BÉLAND, G1J 2G3[2], R. RAHIMIAN, G1J 2G3[2]
[1]Laval Univ., Quebec, QC, Canada; [2]Univ. Laval, Quebec City, QC, Canada

Abstract: Microglia are the principal immune cells of the brain. Once activated, in injured and/or diseased brain, microglia can acquire a wide repertoire of the context-dependent immune profiles. However, at present, the molecular mechanisms involved in the control of microglia polarization profiles remain elusive. By using an in vivo model-system for analysis of the the dynamic translational state of microglial ribosomes with mRNAs as input and newly synthesized peptides as an output, recently created in our laboratory (Boutej et al. Cell Rep 2017),we found a marked dissociation of microglia mRNA and protein molecular signatures following an acute innate immune challenge. The results revealed that highly up-regulated and ribosome-associated mRNAs were not translated resulting in creation of two distinct microglia molecular signatures: i) a highly specialized pro-inflammatory mRNA and ii) immunomodulatory/homeostatic protein signature. The most striking divergence was observed in the key immune NF-κB network where we found that the cluster of highly up-regulated LPS-induced and polysome-associated mRNAs such as Saa3, Lcn2 ccl3, ccl5 (from 15-30 fold increase at mRNA level) were indeed not translated. As mechanism, we discovered a selective 3'UTR-mediated translational suppression of highly expressed mRNAs. Moreover, we identified a novel and previously unknown role for

RNA binding protein SRSF3 as a master suppressor/regulator of innate immune genes translation. The complex analysis of mRNA/protein networks in chronically activated microglia suggest existence of a similar ribosome-based mechanism/check point involved in the control of highly regulated mRNAs *in vivo*.

Disclosures: J. Kriz: None. **H. Boutej:** None. **L. Béland:** None. **R. Rahimian:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.11/T16

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01HL126523
P01HL090554t

Title: Post-inspiratory complex (pico) rhythm irregularities after neuroinflammation

Authors: *I. M. AGOSTO[1], J. RAMIREZ[2]
[1]Seattle Children's Res. Inst., Seattle, WA; [2]Neurolog. Surgery, Univ. Washington, Seattle, WA

Abstract: Studies link neuroinflammation to devastating syndromes such as sudden infant death syndrome (SIDS), epilepsy, autism and many others. Infants are particularly susceptible to pathogens that can lead to neuroinflammation, for this reason this set of studies focuses on how neuroinflammation affects the neonatal medullary region. The medullary region contains neuronal populations necessary for respiration, cardiorespiratory coupling and swallowing. We tested how neuroinflammation affects two areas in the respiratory network, the pre-Bötzinger Complex (PreBötC) and the post-Inspiratory Complex (PiCo), in-vivo and in-vitro. We injected lipopolysaccharide (LPS, 3ug/g) to elicit a systemic inflammation, which leads to up-regulation of key pro-inflammatory cytokines (TNF-α (19-fold change), IL1β (10-fold change) at the medulla. In-vivo respiratory changes were characterized pre- and post-LPS injection using whole body plethysmograph. Three hours after the LPS insult, mice have significant changes in breaths per minute (BPM), interevents intervals (sec) and increase in apneic events ($P<0.05$). These mice are then characterized in population recordings from horizontal, medullary slices. This preparation keeps a large population of the respiratory column intact and includes the PreBötC and PiCo. Our in-vitro data showed a significant frequency increase in the PiCo area. Multiple bursts per respiratory cycle were generated in the absence of exogenously applied norepinephrine. By contrast, the PreBötC showed no significant changes after neuroinflammation. During hypoxic exposure PiCo activity is inhibited, which was associated with a temporary normalization of respiratory activity in vivo. Our findings suggest that

neuroinflammation specifically activates PiCo, which contributes to significant breathing disturbances manifested during the expiratory phase.

Disclosures: I.M. Agosto: None. **J. Ramirez:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.12/T17

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NINDS R01NS089688
NIH NINDS R01NS062019
NIH NINDS R01NS094396

Title: A time course study of melatonin's effect on microglia responses to neural implants as revealed by two-photon imaging

Authors: *Q. YANG, X. PAN, A. GOLABCHI, J. ELES, T. D. Y. KOZAI, X. T. CUI
Univ. of Pittsburgh, Oakland, PA

Abstract: The inflammatory responses of brain tissue greatly hindered chronic applications of neural implants, causing loss of functional neurons and decreased recording quality over time. Melatonin (MT), a compound that is anti-inflammatory, antioxidant and anti-apoptotic, has been demonstrated to improve chronic neural recordings. When comparing chronic melatonin treatment, acute melatonin treatment and saline treatment, we have found that acute melatonin treatment benefits electrophysiological recording initially but the recording quality dropped down shortly after the treatment stopped, while chronic melatonin treatment (daily injection for 16 weeks) maintained high recording quality throughout the implantation period. Postmortem histology at 16 weeks post implant revealed reduced gliosis, decreased oxidative stress and increased neuronal viability in the chronic MT group. However, melatonin's specific effect on immune response during the acute phase is not clear. Here we used two-photon imaging to study the microglia response dynamics after neural probe implantation. 4 shank Michigan electrodes were implanted at 30 degrees in the CX3CR1-GFP transgenic mice cortex. All the animals were grouped for acute melatonin treatment, chronic melatonin treatment and control. We measured the velocity of microglia processes moving toward the implant immediately after neural electrodes insertion. Later on, microglia coverage of the probe surface and the region of activated microglia were traced over time. The imaging was conducted for 4 weeks. At the end time point of study, animals were sacrificed and perfused for further postmortem histology. We found that melatonin administration reduces immediate microglia coverage upon neural electrodes insertion, this data correlates with the higher recording performance (signal-to-noise ratio) in MT

treated compared to the control at the day of surgery. Further chronic imaging gave us the same trend of attenuated microglia infiltration at the implantation site. Characterizing microglia activity between different dosing will help uncover the mechanism of action for melatonin and guide future therapeutic strategies aimed at improving neural electrode-tissue interface.

Disclosures: Q. Yang: None. **X. Pan:** None. **A. Golabchi:** None. **J. Eles:** None. **T.D.Y. Kozai:** None. **X.T. Cui:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.13/T18

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NSF Phase I SBIR award 1549126
NIH Phase I SBIR award 1R43TR001286-01A1
Marcus Center for Therapeutic Cell Characterization and Manufacturing
The Georgia Tech Foundation
The Georgia Research Alliance

Title: Neuroimmune activation and off-target toxicity testing of cell therapies using a novel brain-on-a-chip system

Authors: *J. T. SHOEMAKER[1], J. VUKASINOVIC[1], C. XU[2], Z. WEN[2], M. C. LAPLACA[3]
[1]Lena Biosciences, Inc., Atlanta, GA; [2]Dept. of Psychiatry and Behavioral Sci., Emory Univ. Sch. of Med., Atlanta, GA; [3]Georgia Inst. of Technol., Atlanta, GA

Abstract: Adoptive cellular therapies such as chimeric antigen receptor T (CAR-T) cell therapy have become a promising avenue for cancer treatment. However, unexpected off-target effects of treatment resulting in brain edema and neurotoxicity have raised concern as to how the safety of these therapies can be adequately assessed. Animal models have been ineffective for predicting such events as they require humanized immunodeficient mice for testing. In vitro models are insufficient in that they are often too short-lived and lack the complexity required to accurately recreate the human neural environment. Lena Biosciences has created a novel brain-on-a-chip system comprising human neurons, astrocytes, and microglia in a three-dimensional (3D) scaffold that models neuroinflammation. iPSC-derived neurons and astrocytes were co-cultured with cells from the human microglia cell line HMC3 in SeedEZ scaffolds. Cell viability was high after two weeks in culture. A pro-inflammatory response was confirmed by gene expression and protein release from cultures of microglia and co-cultures of astrocytes and microglia in response to treatment with lipopolysaccharide and interferon gamma. Complete cultures containing neurons were exposed to conditioned medium from activated Jurkat cells or from activated

primary human T cells. Both treatments resulted in a significant increase in the release of pro-inflammatory cytokines and chemokines, with the latter treatment proving to be more potent. Experimental conditions for individual experiments were in triplicate and the studies were repeated to confirm the results. These data validate this as a model of neuroinflammation that can be used to test new therapeutics. Preliminary data exploring the effects of adding perfusion to the 3D cultures has consistently shown improved cell viability and increased metabolic activity. Studies assessing the effects of perfusion on markers of neuroinflammation are ongoing. Additionally, the planned integration of iPSC-derived microglia is expected to enhance the induced neuroimmune response, further improving the relevance of the model. The immense promise of treatments such as CAR-T cell therapy necessitates the creation of preclinical models that can accurately predict off-target effects. Lena Biosciences' brain-on-a-chip system will serve as an invaluable tool for this application as well as any research focused on the mechanisms of neuroinflammation.

Disclosures: J.T. Shoemaker: A. Employment/Salary (full or part-time):; Lena Biosciences, Inc. **J. Vukasinovic:** A. Employment/Salary (full or part-time):; Lena Biosciences, Inc.. **C. Xu:** None. **Z. Wen:** None. **M.C. LaPlaca:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.14/U1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: GSK
The Wellcome Trust (Grant number: 104025/Z/14/Z).

Title: Investigation of TSPO as a target for imaging neuroinflammation

Authors: *M. VICENTE-RODRIGUEZ[1,2], N. SINGH[1], C. SIMMONS[1,2], K. RANDALL[1,2], A. HAJI-DHEERE[3], W. NIMA CONSORTIUM[2], F. TURKHEIMER[1,2], C. A. PARKER[4,2], D. CASH[1,2]
[1]King's Col. London, London, United Kingdom; [2]The Wellcome Trust Consortium for the Neuroimmunology of Mood Disorders and Alzheimer's Dis. (NIMA), London, United Kingdom; [3]PET Centre, St Thomas' Hosp., London, United Kingdom; [4]Exptl. Med. Imaging, GlaxoSmithKline R&D, Stevenage, United Kingdom

Abstract: Mitochondrial TSPO (18-kDa Translocator protein) is a widely used *in vivo* imaging biomarker of neuroinflammation in humans by Positron emission tomography (PET). TSPO has generally been labelled a 'biomarker of neuroinflammation' or 'microglia activation'. However, this is controversial as TSPO is expressed in various CNS and non-CNS cell types including

microglia, astrocytes, macrophages and endothelial cells in response to a variety of insults, as well as in neurodegenerative diseases, which complicates the interpretation of TSPO PET imaging. [^{11}C]PK11195 is a TSPO PET ligand that represents one of the most used imaging biomarkers for detecting inflammation in the CNS. This study aimed to characterise TSPO as an imaging biomarker of neuroinflammation using radiolabelled PK11195 in a rat model of neuroinflammation induced by intracranial LPS, which is known to induce a focal inflammatory reaction. All experiments were ethically reviewed and performed in accordance with the UK Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals. *In vivo* microPET data demonstrated a significantly higher uptake of [^{11}C]PK11195 in the LPS-injected side vs the non-injected side 24 hours following administration. TSPO mRNA and protein expression were also both found to have increased in the lesioned side of the brain 24 hours following the intracranial administration of LPS compared with the non-lesioned side. Additionally, after the intracranial administration of LPS, the increased expression of TSPO was demonstrated to co-localise with both Iba1 positive and negative cells, suggesting its presence in microglia/macrophages as well as other type of cells. Taken together, these findings suggest that TSPO PET signal could be labelling activated microglia alongside other immune-cell types in response to the inflammatory insult. Further analysis of the contribution of different cell types to the overall TSPO PET signal is ongoing to accurately characterise TSPO as an imaging marker in neuroinflammation.

Acknowledgements
This study was part funded by GSK and a grant from the Wellcome Trust (Grant number: 104025/Z/14/Z).

Disclosures: M. Vicente-Rodriguez: None. **N. Singh:** None. **C. Simmons:** None. **K. Randall:** None. **A. Haji-Dheere:** None. **W. NIMA Consortium:** None. **F. Turkheimer:** None. **C.A. Parker:** None. **D. Cash:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.15/U2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Nature Science Foundation of China, No.81473374
National Nature Science Foundation of China, No.81673411
National Nature Science Foundation of China, No.81670474
Beijing New-star Plan of Science and Technology, No.xx2013065
Key Laboratory of Uighur Medicine Foundation of Xinjiang Uygur Autonomous Region, No.2015KL005
Nature Science Foundation of Beijing, No.7152043

Title: Luteolin inhibits fibrillary beta-amyloid$_{1-40}$-induced inflammation ina human blood-brain barrier model by suppressing the p38 MAPK-mediated NF-kappaB signaling pathways

Authors: *R. LIU[1], J. ZHANG[2], J. XING[3], L. WANG[2], H. JIANG[2], S. GUO[4]
[1]Inst. of Materia Medica, Beijing, China; [2]Inst. of Medicinal Biotechnology, Chinese Acad. of Med. Sci. and Peking Union Med. Col., Beijing, China; [3]Xinjiang Inst. of Materia Medica, Urumqi, China; [4]Beijing Friendship Hospital,Capital Med. Univ., Beijing, China

Abstract: Aims: Amyloid-β peptides (Aβ) exist in several forms and are known as key modulators of Alzheimer's disease (AD). Fibrillary Aβ (fAβ) has been found to disrupt the blood-brain barrier (BBB) by triggering and promoting inflammation.
Main methods: In this study, luteolin, a naturally occurring flavonoid that has shown beneficial properties in the central nervous system, was evaluated as a potential agent to preserve barrier function and inhibit inflammatory responses at the BBB that was injured by fAβ1-40. We established an in vitro BBB model by co-culturing human brain microvascular endothelial cells (hBMECs) and human astrocytes (hAs) under fAβ1-40-damaged conditions and investigated the effect of luteolin by analyzing cellular toxicity, barrier function, cytokine production and inflammation-related intracellular signaling pathways.
Key findings: Our results demonstrated that, in cells injured by fAβ1-40, luteolin increased cell viability of hBMECs and hAs. The cytoprotection of the co-culture against the damage induced by fAβ1-40 was also increased at both the apical and basolateral sides. Luteolin protected the barrier function by preserving transendothelial electrical resistance and relieving aggravated permeability in the human BBB model after being exposed to fAβ1-40. Moreover, in both the apical and basolateral sides of the co-culture, luteolin reduced fAβ1-40-induced inflammatory mediator and cytokine production, including cyclooxygenase-2 (COX-2), tumor necrosis factor α (TNF-α), inter leukin1 β (IL-1β), inter leukin6(IL-6), and inter leukin8(IL-8), however it did not show sufficient effects on scavenging intracellular reactive oxygen species (ROS) in hBMECs and hAs. The mechanism of BBB protection against fAβ1-40-induced injury may be related to the regulation of inflammatory signal transduction, which involves inhibition of p38 mitogen-activated protein kinase (MAPK) activation, downregulation of phosphorylated inhibitory κB kinase (phosphor-IKK) levels, relief of inhibitory κB α (IκBα) degradation, blockage of nuclear factor κB (NF-κB) p65 nuclear translocation, and reduction of the release of inflammatory cytokines. Moreover, the employment of p38 MAPK and NF-κB inhibitors reversed luteolin-mediated barrier function and cytokine release.
Significance: Taken together, luteolin may serve as a potential therapeutic agent for BBB protection by inhibiting inflammation following fAβ1-40-induced injury.

Disclosures: R. Liu: None. **J. Zhang:** None. **J. Xing:** None. **L. Wang:** None. **H. Jiang:** None. **S. Guo:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.16/U3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NS083164
AG056924
NC TraCS ECBR 004

Title: Inflammation-associated release of MMP-9 increases neuronal vulnerability in an *in vitro* model of early Alzheimer pathogenesis

Authors: T. DEMARSE[1], T. J. COHEN[2], P. R. CARNEY[3], *R. B. MEEKER[3]
[1]Neurol., Univ. of North Carolina, Chapel Hill, NC; [2]Neurol., Univ. of North Carolina - Chapel Hill, Chapel Hill, NC; [3]Neurol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Matrix metalloprotese-9 (MMP-9) is a zinc-dependent enzyme with widely diverse functions including contributions to normal synaptic plasticity. However, in degenerative diseases such as Alzheimer disease, chronic inflammatory conditions promote excessive secretion of MMP-9 by mononuclear phagocytes. The actions of this MMP-9 leads to neural dysfunction but the mechanisms are not well understood. To better understand the impact of factors secreted by microglia, we cultured primary mouse microglia and human monocyte-derived macrophages and challenged them with oligomeric Abeta. Medium from these cells was applied to 12-28 day old primary mouse cortical/hippocampal neurons grown on microelectrode arrays (MEAs) or coverslips. Factors released from the microglia induced a destabilization of neuronal calcium homeostasis 5-10-fold greater than that of Abeta oligomers alone. Exposure to Abeta conditioned media modified population bursting dynamics and increased firing rates for some neurons while decreasing rates in others. Results from antibody arrays and unbiased proteomic screens verified robust release of MMP-9 which was subsequently quantified at 40-65 ng/ml using a DQ gelatin based assay. The effects of the conditioned medium were partially inhibited by MMP-9 Inhibitor I and enhanced by a neutralizing antibody to tissue inhibitor of metalloprotease-1 (TIMP-1). Direct application of 20 ng/ml activated MMP-9 to the neurons resulted in an increase in NMDAR-dependent calcium signaling and a modest increase in firing rates with a transition to highly synchronous and more periodic burst dynamics. MMP-9 alone was minimally toxic but sensitized neurons such that a subsequent challenge with a low concentration of glutamate (1 μM) evoked pathological increases in calcium and associated structural damage. The p75 neurotrophin receptor ligand, LM11A-31, shifted the macrophage secretome toward increased relative expression of tissue inhibitor of metalloprotease-1 (TIMP-1) thereby reducing MMP-9 activity and associated neural damage. Thus, MMP-9 release in

response to inflammation at early stages of disease primes the nervous system for development of hyperactivity and aberrant network activity. Targeting therapies to these early effects may have the potential to slow disease progression.

Disclosures: T. DeMarse: None. **T.J. Cohen:** None. **P.R. Carney:** None. **R.B. Meeker:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.17/U4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Glucose enhances endothelial cell-mediated activation of a pro-inflammatory phenotype in BV-2 microglia *in vitro*

Authors: *J. M. IANNUCCI[1,2], H. VITTAL RAO[1], P. GRAMMAS[1]
[1]George and Anne Ryan Inst. for Neurosci., [2]Interdisciplinary Neurosci. Program, Univ. of Rhode Island, Kingston, RI

Abstract: Diabetes has been identified as a strong risk factor for the development of Alzheimer's disease (AD). Neuroinflammation mediated by microglia has also been indicated in AD pathology. Microvascular complications in diabetes have been correlated with alterations in glucose control. Additionally, research has suggested a link between endothelial cell changes and neuroinflammation. We hypothesize that injury to endothelial cells by glucose and other noxious stimuli will induce a pro-inflammatory phenotype in microglia. Human brain microvessel endothelial cells (HBMVECs) and BV-2 microglia were grown *in vitro*. HBMVECs were divided into three treatment groups: control, glucose, and mannitol. Each of those three groups had four sub-treatment groups: normoxia, hypoxia, thrombin, thrombin+hypoxia. Following treatment, HBMVEC supernatant was collected and used to treat BV-2 microglia for 24 hours. At the end of 24 hours, MTT was used to determine cell viability, and Griess assay was used to measure nitric oxide (NO) production. MMP-9 and MMP-2 activity were measured using gel zymography, and Western Blot assessed TNFα and IL-6. Treatment with supernatant from glucose-treated HBMVECs induced a pro-inflammatory phenotype in BV-2 microglia characterized by increased NO production ($p<.0001$ vs. untreated control), increased MMP-9 activity, and increased TNFα and IL-6. The level of pro-inflammatory activation was correlated with the extent of endothelial cell injury, with the glucose-thrombin+hypoxia group showing the greatest increase in NO production ($p<.0001$ vs. glucose only) and MMP-9 activity. Overall, our results show that treatment with supernatant from injured endothelial cells induces a pro-inflammatory phenotype in microglia that is enhanced in the presence of glucose. This suggests a link between endothelial cell injury in diabetes-like conditions and the activation of a pro-

inflammatory phenotype in microglia in the brain. Further studies could help to determine the signaling mechanisms behind this phenotypic switch.

Disclosures: J.M. Iannucci: None. **H. Vittal Rao:** None. **P. Grammas:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.18/U5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Lundbeck Fonden
Fonden til Lægevidenskabens Fremme

Title: Increased vascular density in an experimental rat model with neurodegeneration and inflammation

Authors: *M. S. THOMSEN, L. J. ROUTHE, S. S. HELGUDÓTTIR, T. MOOS
Aalborg Univ., Aalborg Ost, Denmark

Abstract: Introduction: The blood-brain barrier (BBB) represents the interface between the blood and brain parenchyma, and is important for ensuring sufficient nutrient transport and for maintaining brain homeostasis. Many conditions with neurodegeneration and inflammation are accompanied by changes of the BBB, including increased BBB permeability and changes of the vascular basement membrane. We have previously in an experimental model of neurodegeneration shown that excitotoxic-induced neurodegeneration in substantia nigra pars reticulata (SNpr) was accompanied by activation of microglial cells and infiltration of inflammatory cells. We therefore aimed to investigate if the neurodegeneration with inflammation is associated with changes of the BBB using the same model. Method: The model of neurodegeneration with inflammation was created by stereotactical injection of ibotenic acid into the left striatum, which subsequently results in excitoxicity in the left SNpr (lesioned side). We examined changes of the BBB by injection of 3 and 10 kDa Texas Red™-Lysine Fixable-Dextrans 4 minutes before termination and immunolabeling of endogenous albumin. Changes of the basement membrane proteins Fn1, Col4a1, Lama2, Lama4, Lama5 were investigated using RT-qPCR analysis. Results/conclusion: In response to the induced neurodegeneration with inflammation a significant increase in vascular density was observed in the lesioned side compared to the non-lesioned side. Furthermore, parenchymal labelling of albumin in the lesioned side indicates increased BBB permeability. There was no change in the gene expression of the basement membrane proteins Fn1, Lama2, Lama4, and Lama5, however the expression of Col4a1 was significantly decreased in both lesioned and non-lesion SNpr compared to SNpr

from aged matched control animals. Together, these results indicate that the BBB is greatly affected in conditions with chronic neurodegeneration and inflammation.

Disclosures: M.S. Thomsen: None. **L.J. Routhe:** None. **S.S. Helgudóttir:** None. **T. Moos:** None.

Poster

658. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Microglia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 658.19/U6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: The Ministry of Science and Technology of Taiwan Grant 106-2320-B-002-007-MY3

Title: The role of equilibrative nucleoside transporter-2 in the modulation of neuroinflammation

Authors: *C.-Y. LEE, K.-C. WU, Y.-H. KAO, C.-J. LIN
Sch. of Pharmacy, Col. of Med., Natl. Taiwan Univ., Taipei, Taiwan

Abstract: Neuroinflammation is a common characteristic of many neurodegenerative disorders. Adenosine is an endogenous anti-inflammatory agent and its extracellular level in the brain may play an important role in modulating the status of neuroinflammation. The equilibrative nucleoside transporters, ENT1 an ENT2, are the major membrane transporters responsible for cellular uptake of adenosine and the maintenance of extracellular adenosine level in the brain. Given that the expression of ENT2 is higher than that of ENT1 in the brain of mice, in the present study, ENT2 knockout (KO) mice were established and used to clarify the roles of ENT2 in modulating neuroinflammation induced by the treatment of lipopolysaccharide (LPS). The results showed that ENT2 KO significantly ameliorated the LPS-induced neuroinflammation, in terms of the increase of cytokine levels, astrogliosis and microglia activation. The results of in-vivo brain microdialysis study confirmed that LPS treatment increased extracellular levels of adenosine and the extent of increase in extracellular adenosine levels were significantly higher in ENT2 KO mice than in the littermate controls. Taken together, these findings suggest that ENT2 plays a crucial role in maintaining extracellular adenosine and adenosine-mediated neuroprotection in LPS-induced neuroinflammation.

Disclosures: C. Lee: None. **K. Wu:** None. **Y. Kao:** None. **C. Lin:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.01/U7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: This work was partially supported by CONACYT Grant 2012-CB-01-177594.

Title: Protein expression profile of IL-1ß, phosphorylated p38 and VEGF-A in the hippocampus after 4-aminopyridine-induced seizures in adult mice

Authors: *M. E. URENA-GUERRERO[1], J. L. CASTAÑEDA-CABRAL[1], J. MURGUÍA-CASTILLO[1], B. GARCÍA-SANTIAGO[1,2], C. BEAS-ZÁRATE[1]
[1]Univ. de Guadalajara (CUCBA), Zapopan, Jalisco, Mexico; [2]Univ. de la Sierra de Juárez, Oaxaca, Mexico

Abstract: Recent evidence suggests that excessive neuronal activity in non-infectious pathological processes (as seizures) may induce an inflammatory response in the brain. In this sense, it is known that IL-1β mRNA expression level and its immunohystochemical reactivity are both increased by seizures; and that IL-1β-mediated signaling activation promotes the seizures and its blocking reduces them. The goal of this work was to establish a temporal course of the IL-1β protein expression in the hippocampus following the 4-aminopyridine (4AP)-induced *status epilepticus* (SE) onset in adult mice through ELISA quantitative assay (ELISAq) confirmed by western-blotting. Moreover in the same samples, phosphorylated p38 and VEGF-A protein expression levels were determined by western-blotting too. The study was performed in adult CD1 male mice of 25-30 g of body weight (b.w.). First, we established that 4AP 10.75 mg/kg of b.w. administered intraperitoneally was able to produce SE in 60% of the animals without dying. After that, 5 animals were sacrificed to obtain the hippocampus at 0, 0.5, 1.5, 3, 6, 12, and 24 h after SE onset by that 4AP dose. ELISAq assay showed that the IL-1β level at time 0.5 h was almost two-fold higher than the basal observed at time 0 h (without 4AP), and at time 1.5 h the IL-1β level reached a peak in four-fold higher than the basal. After that, the IL-1β level decreased to reach the basal at time 6 h, but increasing again at time 24 h almost at the same level of the peak. Western-blotting to IL-1β confirmed the temporal course described above, but the increases were more pronounced. Following the peak of IL-1β, phosphorylated p38 and VEGF-A protein expression levels increased to reach a peak at times 3 h and 6 h, respectively. Results indicates that IL-1β increase could trigger both cell death and angiogenesis process, and suggests that blocking IL-1β must be broadly studied as a putative strategy to avoid epileptogenesis process.

Disclosures: M.E. Urena-Guerrero: None. **J.L. Castañeda-Cabral:** None. **J. Murguía-Castillo:** None. **B. García-Santiago:** None. **C. Beas-Zárate:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.02/U8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Israeli Ministry of Science and Technology
Jacobs Foundation Fellowship
Howard Hughes Medical Institute (HHMI)
Wellcome Trust
Prince Center for Neurodegenerative Diseases

Title: Effects of short term sleep deprivation on the brain's immune compartment

Authors: *B. KORIN[1], S. AVRAHAM[2], H. AZULAY-DEBBY[1], F. HAKIM[3,4], A. ROLLS[1]
[1]Dept. of Neuroscience, Dept. of Immunol., [2]Dept. of Cell Biol. and Cancer Sci., Technion - Israel Inst. of Technol., Haifa, Israel; [3]Pediatric Pulmonary Div., Rambam Hlth. Care Campus, Haifa, Israel; [4]Cancer Res. Center, EMMS Hosp., Nazareth, Israel

Abstract: A normal sleep cycle is vital for body and brain homeostasis, and many neurodegenerative diseases are accompanied by sleep disorders and immune dysfunction. The immune system in the brain compartment is comprised of multiple immune cell types that constantly interact with the neural tissue. We recently showed, using mass cytometry (CyTOF), the diversity of immune cells that are present even in the naïve mouse brain. Here, with mass cytometry, we characterize the immune cells of the brain compartment (i.e., the parenchyma, meninges and choroid plexus) following short term sleep deprivation (6 hours). We illustrate the alterations in immune cell composition and phenotype in the mouse brain, caused by sleep deprivation. We show that the abundance of the various immune populations remains largely un-affected. However, the expression pattern of functional, intracellular and extracellular markers is altered in several cell types, mainly, macrophages and natural killer (NK) cells. As sleep deprivation is a prevalent comportment of the modern world, our data may have relevant implications to the effects of sleep deprivation on normal and pathological brain function.

Disclosures: B. Korin: None. **S. Avraham:** None. **H. Azulay-Debby:** None. **F. Hakim:** None. **A. Rolls:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.03/U9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NS082092

Title: The role of lysophosphatidic acid in post-hemorrhagic hydrocephalus

Authors: *P. SANCHEZ PAVON[1,2], V. A. BLAHO[1], N. LUMMIS[1,3], J. CHUN[1]
[1]SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INSTITUTE, La Jolla, CA; [2]Sanford Burnham Prebys Med. Discovery Inst. Grad. Sch. of Biomed. Sci., La Jolla, CA; [3]Univ. of California San Diego Biomed. Sci. Grad. Program, La Jolla, CA

Abstract: Post-hemorrhagic hydrocephalus (PHH) is a neurological disease that primarily affects premature infants (~1 in 1000 births). It is characterized by an increase in intracranial pressure, enlargement of the brain ventricles (ventriculomegaly), accumulation of cerebrospinal fluid (CSF), and a representative dome-shaped head deformation. The current treatment involves the surgical introduction of a shunt into the brain ventricles to redistribute the excess of CSF into the patient's stomach, where it can be reabsorbed. Lysophosphatidic acid (LPA) is a bioactive lipid present in blood that signals through 6 known G-protein coupled receptors (GPCRs). Injection of LPA into the brain ventricles has previously been shown to initiate hydrocephalus. Previous studies in our laboratory using a neonatal PHH model have linked the development of PHH to the disruption of the ependymal cell barrier. These cells surround the ventricles and are responsible for the correct flow of the CSF. In addition to the loss of the ependymal layer, we have observed immune cell brain infiltration at different time points after LPA injection. To address the correlation between these two events we will test the hypothesis that immune cells are recruited by LPAR-mediated ependymal cell death, promoting a prolonged inflammatory environment that aggravates PHH. Temporal changes in immune cell number and population collected from whole mouse brain will be assayed by flow cytometry at different points in time post-LPA injection. We will also genetically and pharmacologically target LPA receptors (LPARs) to resolve their effect in ependymal cell integrity, immune cell infiltration and progression of PHH. This approach aims to reduce the need for CSF shunting and define a therapeutically tractable target cell type(s) at specific times post-PHH leading to improved quality of life for hydrocephalus patients.

Disclosures: P. Sanchez pavon: None. **V.A. Blaho:** None. **N. Lummis:** None. **J. Chun:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.04/U10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: APP108197

Title: Peripheral macrophage infiltration post-stroke in the primate is attenuated by reactive astrocytes through NogoA-LILRB2 mediated signalling

Authors: *A. G. BOGHDADI[1], L. TEO[1], B. CAO[1,2], S. M. STRITTMATTER[3], S. K. NILSSON[1,2], J. A. BOURNE[1]
[1]Australian Regenerative Med. Inst., Monash Univ., Clayton, Australia; [2]CSIRO, Clayton, Australia; [3]CNNR Program, Yale Univ., New Haven, CT

Abstract: Blood brain barrier breakdown post-stroke results in peripheral immune cell infiltration, leading to an acute inflammatory response. Previous studies have demonstrated that reactive astrocytes can directly limit immune cell infiltration, thereby attenuating the inflammatory response post-stroke. A major immune modulator, leukocyte immunoglobulin like receptor 2 (LILRB2) is a MHC1 class receptor expressed on peripheral immune cells in primates, including humans. Upregulated neurite outgrowth inhibitor A (NogoA) post-stroke by glia is a major activator of LILRB2 signaling. This study explores the interaction between astrocytes and macrophages involving NogoA and LILRB2 at specific, acute time points post-stroke in the nonhuman primate neocortex.
Injections of 0.5uL endothelin-1 (1mg/mL) over 4 sites surrounding the posterior cerebral artery of operculum primary visual cortex (V1) in adult marmosets (>1 year; n=24) were used to induce stroke. Control, 1-day post injury (DPI), 7 DPI and 21 DPI brains were snap-frozen (n=12) or fixed (n=12) for downstream analysis. The human monocyte cell line (ATCC; TIB-202) was differentiated to represent infiltrating macrophages post-stroke. Western blot, immunohistochemistry, immunofluorescence and *in vitro* techniques were used to analyze the ligand-receptor interaction *ex vivo* and *in vitro*.
Elevated NogoA/LILRB2 expression was observed in marmoset V1 (peri-infarct) 7-21 DPI. LILRB2 labelled a distinct subpopulation of Iba1+/TMEM119- infiltrating macrophages at the lesion site at 7 DPI. Concurrently, NogoA labelled a distinct, complementary subpopulation of GFAP+ reactive astrocytes, juxtaposing LILRB2+ macrophages, proximal to the lesion site. NogoA expression on reactive astrocytes was downregulated by 21 DPI, corresponding to more discrete distribution of LILRB2+ macrophages in V1. Recombinant human NogoA (566-748aa) Fc-coated stripes significantly induced human macrophage cell repulsion *in vitro*. NogoA-induced repulsion was abrogated by pretreatment of macrophages with a LILRB2 blocking

antibody
These findings provide evidence of a novel NogoA/LILRB2 dependent, anti-inflammatory interaction between reactive astrocytes and infiltrating macrophages in the acute stages post-stroke in primates. Specifically, NogoA+ astrocytes limit the infiltration of LILRB2+ macrophages into underlying healthy brain tissue post-stroke. The implications of these findings are particularly significant in light of recent NogoA-based therapeutic strategies, especially in the context of treatment administration time, which can adversely affect endogenous repair mechanisms.

Disclosures: A.G. Boghdadi: None. **L. Teo:** None. **B. Cao:** None. **S.M. Strittmatter:** None. **S.K. Nilsson:** None. **J.A. Bourne:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.05/U11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant U01-AA020935 (ALM)
NIH grant R01-AA024095 (ALM)
R01-AA021261 (LA)
the Bowles Ctr for Alcohol Studies (ALM)

Title: Protective effects of the endogenous neurosteroid (3α,5α)3-hydroxypregnan-20-one (3α,5α-THP) on proinflammatory TLR4 signaling in immune cells and brain

Authors: *I. BALAN[1], M. C. BEATTIE[2], T. O'BUCKLEY[2], L. AURELIAN[1], A. L. MORROW[2]
[1]Pharmacol., Univ. of Maryland Baltimore, Baltimore, MD; [2]Dept. of Psychiatry and Pharmacology, Bowles Ctr. for Alcohol Studies, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Activation of toll-like receptor 4 (TLR4) signaling pathways plays a significant role in the pathogenesis of alcoholism, depression, traumatic brain injury, schizophrenia, multiple sclerosis, and Alzheimer's disease. The endogenous neurosteroid (3α,5α)3-hydroxypregnan-20-one (3α,5α-THP, allopregnanolone) has protective activity in these conditions, but its mechanism of action is still poorly understood. Until recently TLR4 signaling was believed to be limited to glial cells in the brain. It is now known that neurons also express TLR4, but the mechanism of TLR4 activation and signaling outcomes and the role of 3α,5α-THP in the TLR4 signal regulation in neurons are still poorly understood. To test the possibility that 3α,5α-THP inhibits proinflammatory neuroimmune signaling in the periphery and the brain, we examined the effects

of 3α,5α-THP on agonist (LPS)-induced TLR4 signal activation in immune cells (RAW264.7), as well as on the innately activated TLR4 signal in the ventral tegmental area (VTA) of selectively bred alcohol-preferring P rats. LPS activated the TLR4 signal in RAW264.7 cells as evidenced by increased levels of pTAK1, TRAF6, NFkB p50, phospho-NFkB-p65, pCREB, HMGB1, and inflammatory mediators, including MCP-1 and TNFα. 3α,5α-THP (0.5-1.0μM) substantially (~80%) inhibited these effects, indicating pronounced inhibition of TLR4 signaling. The mechanism of inhibition appears to involve blockade of TLR4/MD-2 protein interaction. In P rat VTA, 3α,5α-THP (15 mg/kg, IP) administration reduced TRAF6 (~20%), CRF (~30%), and MCP-1 (~20%) levels, as well as TLR4 binding to the $GABA_A$ receptor α2 subunit (~60%) and MyD88 (~40%). We found that LPS does not activate the TLR4 signal in the neuronal N2a cells, as evidenced by the failure to increase the levels of both phospho-NFkB-p65 and pCREB. By contrast, the pCREB levels and its nuclear translocation were significantly increased in the $GABA_A$ α2-transfected N2a cells, indicating that $GABA_A$ α2 activates the TLR4 signal in neurons. The $GABA_A$ α2-activated TLR4 signal was also inhibited by 3α,5α-THP in N2a cells through blocking of the interaction between the TLR4 and $GABA_A$ α2 proteins. The data identify the role of α2 and its ability to interact with TLR4 in neuronal TLR4 activation and document that inhibition of proinflammatory neuroimmune TLR4 signaling underlies protective effects of 3α,5α-THP in immune cells and brain, apparently involving blocking of protein-protein interaction.

Disclosures: I. Balan: None. **M.C. Beattie:** None. **T. O'Buckley:** None. **L. Aurelian:** None. **A.L. Morrow:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.06/U12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01 NS097776
U01 NS05158

Title: Conditional knockout strategies reveal opposing effects of prostaglandin receptor EP2 signaling in immune cells and neurons after status epilepticus

Authors: *N. H. VARVEL[1], D. CHEN[2], A. BIEGEL[2], R. J. DINGLEDINE[3]
[1]Pharmacol., Emory Univ., Atlanta, GA; [2]Dept. of Pharmacology, Emory Univ., Atlanta, GA; [3]Dept Pharmacol, Emory Univ. Sch. Med., Atlanta, GA

Abstract: Status epilepticus (SE) is a life-threatening medical emergency that triggers a succession of molecular and cellular events culminating in blood brain barrier (BBB) leakage,

activation of brain microglia, and infiltration of blood-borne monocytes into brain. Long-standing unresolved issues are how these adverse consequences of SE contribute to the debilitating neurobehavioral deficits that decrease quality of life in afflicted individuals. Previous studies in our group have identified neuron-derived prostaglandin E2 production and subsequent activation of prostaglandin receptor EP2 as a driver of SE-induced neuroinflammation and neuronal damage, contributing to mortality and neurobehavioral deficits. More recent work showed that EP2 activation in innate immune cells (monocytes and microglia) drives numerous deleterious consequences of SE including erosion of the BBB, neurobehavioral deficits, and suppression of weight gain. In the present study we sought to identify which effects of EP2 antagonism could be reproduced by conditional neuronal ablation of EP2 receptor via syntaxin promoter expression of Cre recombinase in male C57Bl/6CR mice bearing a floxed EP2 allele. Notably, pilocarpine-induced seizure activity and acute mortality were not different between EP2 conditional knockout animals and EP2-sufficient littermate controls. Surprisingly, elimination of EP2 receptor from forebrain neurons enhanced neuronal injury, selectively elevated induction of pro-inflammatory cytokines, TNFα and Ccl2, but not IL-1β and IL-6, in hippocampus, promoted leakiness of the blood-brain barrier, delayed weight recovery, and negatively affected animal posture and activity four days after pilocarpine-induced SE. Taken together these data highlight the complexities in neuroinflammatory signaling in the brain, wherein activation of EP2 receptor in brain innate immune cells is deleterious, whereas neuronal EP2 signaling is protective. Thus, effective treatments for patients targeting brain prostaglandin signaling pathways should be cell targeted in order to be optimally effective.

Disclosures: N.H. Varvel: None. **D. Chen:** None. **A. Biegel:** None. **R.J. Dingledine:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.07/V1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: AIRC Grant IG 16713

Title: Allostatic conditions of glioblastoma stem cells are maintained by mutual influence of chronic oxidative stress, basic intracellular ph and clic1 protein associated chloride current

Authors: I. VERDUCI, 20133[1], T. FLORIO[2], F. BARBIERI[2], V. CARLINI[1], M. PERETTI[1], F. M. RACITI[1], A. DAGA[3], *M. MAZZANTI[1]
[1]Univ. di Milano, Milano, Italy; [2]Dept. of Intrnl. Medicine, Sect. Pharmacol., Univ. di Genova, Genova, Italy; [3]Terapie Oncologiche Integrate, Ospedale Policlinico San Martino, Genova, Italy

Abstract: Glioblastoma (GB) is the most lethal, aggressive and diffuse among brain tumors. The main challenge for successful treatment is targeting the cancer stem cell (CSC) sub-population, considered the main responsible for tumor origin, progression and recurrence. CSCs lay in a chronic allostatic condition, characterized by upregulation of several molecular pathways and overexpression of membrane proteins. In this context, CSCs show abnormal ROS production and alkaline intracellular pH due to hyper activation of membrane NADPH oxidase and NHE1 proton pump, respectively. Previous experiments demonstrated that oxidative stress promotes the translocation of the chloride intracellular protein 1 (CLIC1) from the cytoplasm to the plasma membrane, where it is responsible for the increment of chloride membrane permeability. CLIC1 is constitutively present in the plasma membrane of CSCs. *In vitro,* CLIC1 inhibition leads to a significant arrest of GB CSCs in G1 phase of the cell cycle. Furthermore, CLIC1 knockdown impairs tumor growth *in vivo*. Here, we demonstrate that CLIC1 membrane localization and function are specific for GB CSCs. Mesenchymal stem cells (MSCs) do not show CLIC1-associated chloride permeability and inhibition of CLIC1 protein function has no influence on MSCs cell cycle progression.
The aim of our investigation is to downregulate the allostasis condition of CSCs to a steady state characteristic of glial cells by impairing CLIC1 membrane activity. Any action directed against the membrane oxidase and the proton pump results in cell death not only of CSCs but also of MSCs. On the contrary, CLIC1 membrane protein inhibition does not kill the cells but elongates cell cycle duration to a proliferative rate similar to control cells. Our results show that CLIC1 membrane protein is crucial and specific for GB CSC proliferation, and is a promising pharmacological target for successful brain tumor therapies.

Disclosures: I. Verduci: None. **T. Florio:** None. **F. Barbieri:** None. **V. Carlini:** None. **M. Peretti:** None. **F.M. Raciti:** None. **A. Daga:** None. **M. Mazzanti:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.08/V2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Fondazione G. Celeghin (Italy) grant 2018

Title: Different biguanide-related drugs eradicate human glioblastoma stem cell through the inhibition of chloride intracellular channel 1 activity

Authors: *T. FLORIO[1,2], F. BARBIERI[2], R. WURTH[2,3], I. VERDUCI[4], M. CATTANEO[5], A. SOLARI[2], A. DAGA[6], L. M. VICENTINI[4], M. MAZZANTI[5]
[1]Dept. of Intrnl. Medicine, sect. Pharmacol., [2]Univ. of Genova, Genova, Italy; [3]Div. of Stem

Cells and Cancer, Deutsches Krebsforschungszentrum, Heidelberg, Germany; [4]Univ. of Milano, Milano, Italy; [5]Univ. di Milano, Milano, Italy; [6]Ospedale Policlinico San Martino, Genova, Italy

Abstract: Drug repositioning is an appealing strategy for drug development. The biguanide metformin, an oral antihyperglycemic agent widely used for the treatment of type 2 diabetes, represents the paradigmatic non-cancer agent showing preclinical and clinical antitumor effects in numerous tumor types. Metformin antiproliferative activity is specifically directed against the cancer stem cell (CSC) subpopulation. CSCs are self-renewing and multipotent cells responsible for development and recurrence of most cancers, including glioblastoma (GBM), the most aggressive primary brain tumor. Metformin exerts antiproliferative effects in GBM CSCs by blocking the chloride intracellular channel 1 (CLIC1) activity inducing cell cycle arrest at the G1-S transition. However, high concentrations (mM range) of metformin are required to affect cancer cell proliferation, hardly transferable to the clinical setting. Therefore, more potent biguanide derivatives deserve further investigation. We tested the antiproliferative efficacy of several known biguanide drugs (phenformin, a withdrawn antidiabetic drug; moroxydine, a former antiviral agent; cycloguanil, used for the prevention of malaria) in GBM CSCs. All the compounds studied significantly impaired GBM CSC proliferation, reaching IC_{50} values lower than metformin (μM range). Cell survival inhibition was accompanied by decreased cell invasiveness in 3D models and correlates to the ability to inhibit CLIC1-mediated ion flux, showing the same higher potency than metformin. These effects were specific toward CSCs since no (or slight) cytotoxicity was observed in differentiated GBM cells and, more importantly, in human normal umbilical cord mesenchymal stem cells. Thus the inhibition of CLIC1 activity represents a biguanide class-effect mechanism of action to suppress CSC viability, proliferation and invasiveness. Despite differences among the dugs tested were observed as far as potency, efficacy and selectivity in inhibiting CLIC1 activity, CLIC1 is the common molecular determinants of all biguanides to specifically target CSCs while sparing normal cells. This high selectivity suggests the rational design of novel molecules containing biguanide moiety, characterized by high antitumor efficacy and safe toxicological profile.

Disclosures: T. Florio: None. **F. Barbieri:** None. **R. Wurth:** None. **I. Verduci:** None. **M. Cattaneo:** None. **A. Solari:** None. **A. Daga:** None. **L.M. Vicentini:** None. **M. Mazzanti:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.09/V3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Rockefeller Neuroscience Institute Intramural
None

Title: Inhibition of glioblastoma cell invasion and survival by targeting integrin beta 1 using anti-tumorigenic novel quinazoline derivatives

Authors: *T. K. KHAN
Rockefeller Neurosciences Inst., Morgantown, WV

Abstract: Glioblastoma multiforme (GBM) is the most common and most malignant (stage IV brain tumors) among all brain tumors (~50% of brain tumors). The median survival rate is ~14.5 months with no disease-modifying curative treatment. Radiation and adjuvant temozolomide (TMZ) chemotherapy after the surgical resection is the first line treatment of GBM. Common side effects of TMZ are bone marrow suppression, genotoxic, and teratogenic. The mechanism of action TMZ is damaging GBM cell by DNA methylation and triggering the death of GBM cells. DNA damage is not specific to GBM cells, as a result, it is genotoxic. Studies found that 60-75% cases have no benefit from TMZ chemotherapy[1]. FDA approved immunotherapeutic agent Bevacizumab (Avaztin, Genentech) produced some improvement including cognitive benefit[2], but 40% of patients developed therapeutic resistance in phase II clinical trial[3].
Here we report inhibition of glioblastoma cells by synthetic quinazoline derivatives as a new therapeutic approach. Novel quinazoline derivatives induced glioblastoma cell death and decreased glioblastoma cell invasion. This specific synthetic compounds induced GBM cell death, stopped the cellular invasion in three dimensional Matrigel matrix, and was highly specific to GBM cell death when tested with other cells. Some of the potent synthetic quinazoline derivatives are non-toxic to normal non-tumorigenic cells but toxic to cancerous cells. Newly discovered novel quinazoline derivatives can be synthesized very easily (less than 4 reaction steps) with very high yields. Most potent quinazoline derivative (6-Pyridin-2-yl-5, 6-dihydro-benzo [4,5]imidazo[1,2-c]quinazoline) was synthesized by one chemical step with 90% yield. Pharmacological intervention to GBM cells by the most potent quinazoline derivative caused increased GBM cell apoptosis and decreased GBM cell invasion by inhibiting β1 integrin. In cell adhesion dynamics integrins and extracellular matrix (ECM) mediate interactions that are required for tumor cells invasion and metastasis. Since the interaction of integrin β1 and ECM protects glioma cells drug-induced anoikis targeting integrin β1 has potential as an antiangiogenic therapy for glioblastoma. Novel quinazoline derivative decreases oncogenic PKC-epsilon activity in neuroblastoma cells. Most potent synthetic quinazoline derivatives can be used as an effective treatment of GBM alone, or in combination with other chemotherapeutic/immunotherapeutic agents.
1. Chamberlain MC. Expert Rev Neurother 2010; 10:1537.
2. Kienast Y, Winkler F. Expert Rev Anticancer Ther 2010; 10:1763.
3. Vredenburgh JJ, et al. Clin Cancer Res 2007; 13:1253.

Disclosures: T.K. Khan: None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.10/V4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Microglial depletion compromises survival, brain growth and sensorimotor reflexes acquisition in mouse pups exposed to perinatal cerebellar insults

Authors: *S. TREMBLAY, A. PAI, W. MENG, D. GOLDOWITZ
CMMT, Vancouver, BC, Canada

Abstract: Background: Extreme preterm infants are exposed to multiple stressors including perinatal cerebellar haemorrhage (CBH) and postnatal infection, two major risk factors for neurodevelopmental impairments. Given microglia involvement in inflammatory functions across the central nervous system, they may play a central role in the pathogenesis of cerebellar injury in developing brains. By using a transgenic mouse model, the role of microglial cells on short-term outcomes in CBH and early inflammation (EIS) will be studied. **Methods:** Conditional transgenic mice dependent on diphtheria toxin (DT) intracerebellar injection to deplete *CX3CR1*-positive cells were made and CBH was induced by a local injection of bacterial collagenase at P2 combined with an intraperitoneal LPS injection to mimic EIS. **Results:** Survival is mainly affected by being exposed to DT (50%) or to CBH (48,6% to 54,6%) compared to control (71,4%) or vehicle-exposed mice (62,6%). *CX3CR1*-depleted mouse pups exposed to combined insults have smaller corrected brain weight compared to *CX3CR1*-depleted mice exposed to single insult (*$P<0.05$). Functional assessment reveals a significant delay of grasping acquisition in *CX3CR1*-depleted pups exposed to EIS compared to non-depleted mice (*$P=0.03$) or *CX3CR1*-depleted pups exposed to vehicle (**$P<0.0053$). **Conclusions:** Microglia-depleted mice exposed to early inflammation have worse neonatal outcomes including compromise survival and a delay in grasping acquisition compared to non-depleted mice, suggesting a potential protective role of microglial cells after EIS insult.

Disclosures: S. Tremblay: None. **A. Pai:** None. **W. Meng:** None. **D. Goldowitz:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.11/V5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: PAPIIT-UNAM IN200913
PAPIIT-UNAM IN201915
PAPIIT-UNAM IN205718

Title: Dehydration-induced anorexia increases microglia density in the rat prefrontal cortex

Authors: *P. REYES ORTEGA[1], A. MARTINEZ-TORRES[2], D. REYES-HARO[3]
[1]Inst. de Neurobiología UNAM, Queretaro, Mexico; [2]INB-UNAM, Queretaro, Mexico; [3]Inst. de Neurobiologia|910003400|0, Querétaro, Mexico

Abstract: Anorexia nervosa is an eating disorder characterized by restrictive caloric intake that induces profound weight loss. The neurobiology of this disorder is unknow, but magnetic resonance imaging studies reported functional and structural alterations in the prefrontal cortex of anorexic patients. Recent studies in murine models of anorexia suggest that glial cells deficits in this region may be linked to alterations observed in patients. Glial cells are the major group in the brain and cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) are released by this cells during neuroinflammation. However, whether anorexia affects microglia is unknown. The aim of this study was to test if microglia of the prefrontal cortex is affected by dehydration induced anorexia (DIA). Methods: Three independent experimental series of seven female Wistar rats (180-200g) per group were used for this study: a) Control: received food and water *ad libitum*, b) DIA: received saline solution (2.5 % NaCl) and food *ad libitum*, c) Forced Food Restricted (FFR) group received water and the same amount of food as the DIA group. Body weight and food intake were monitored daily for 5 days. Subsequently, the rats were euthanized, brain tissue sections (30 μm) were obtained for immunofluorescence studies with the microglia marker Iba-1. Quantitative assessment of microglial density well as TNFα and IL-6 expression was estimated for the three experimental groups. Results: Microglia/nuclei ratio was significantly increased in medial prefrontal cortex of DIA and FFR groups (Control 0.10±0.01, DIA 0.18±0.02, FFR 0.22±0.03; $p = 0.003$; n=7). Likewise, reactive/resting microglia ratio was significantly increased for DIA and FFR (Control 0.70±0.06, DIA 2.14±0.42, 1.89±0.40; $p = 0.04$; n=7). Additionally, Western blots showed that anorexia increases the expression of the TNFα (DIA 1.98±0.1, FFR 1.81±0.08; $p = 0.02$; $n = 3$) and IL-6 (DIA 1.85±0.05, FFR 1.69±0.09; $p = 0.04$; $n = 3$). We conclude that in prefrontal cortex DIA and FFR increase microglia density and expression of TNFα and IL-6.

Disclosures: P. Reyes Ortega: None. **A. Martinez-Torres:** None. **D. Reyes-Haro:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.12/V6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: MEXT KAKENHI 17903802
MHLW KAKENHI 16770039

Title: Autistic neuronal differentiation factors derived from astrocyte and microglia: Variant differentiation of cultured neurosphere in valproate-treated glia-conditioned medium

Authors: C. NISHIKAWA[1], K. SATO[2], N. HOZUMI[1], Y. FUETA[3], S. UENO[3], Y. SEKINO[4], Y. KANDA[2], Y. NOMURA[5], *S. YOSHIDA[1]
[1]Toyohashi Univ. Technol., Toyohashi, Japan; [2]Lab. Neuropharmacol, Div. Pharmacol, Natl. Inst. Hlth. Sci., Kanagawa, Japan; [3]Univ. Occupational/Environmental Hlth., Kitakyushu, Japan; [4]Dept. of Chem. Pharmacol., The Univ. of Tokyo, Grad. Sch. of Pharma, Tokyo, Japan; [5]Psychology, Queens Col. & Grad. Ctr. CUNY, Flushing, NY

Abstract: Autism spectrum disorder (ASD), which is a severe neurodevelopmental disorder, is reported to show cerebral and cerebellar abnormalities. In particular, reduction in size and number of Purkinje cells in the cerebellum is observed in both postmortem human studies, and drug-administrated adult animals. Some antiepileptic drugs, organophosphorus agents, and other inflammatory agents are known as the candidates of the inducer of autism. Therefore, we have observed valproate (VPA) made recognizable structural and functional change in developing rat cerebellar cortex. The rats maternally administered 600 mg/kg VPA p.o. at embryonic day 16 (E16), showed irregular excess folding on lobule V - VII, and mossy Purkinje cell dendrites. Because neuronal differentiation and apoptosis would be controlled by neurotrophic factors and cytokines derived from astrocyte and microglia, microglial condition and releasing molecules could be focused on as a target to study the cause of ASD. Activated microglia is distinguished between two states, M1 or M2. M1-state microglia works to pro-inflammatory, whereas M2 works to neuronal protection. Understanding microglial condition and its factors should provide significant insights into neuronal development.To investigate the molecular mechanism of VPA-induced neuronal malformation, we examined the interaction of VPA-administered rat cerebellar glial cells with the differentiation of cerebral neurosphere and compared normal glia. Neurosphere derived from E16 rat cerebrum was differentiated on the confluent glial cells derived from native or VPA-administrated newborn rats. In some cases, we prepared the glia-conditioned differentiation medium (GCM) from the confluent glial sheet. Neurosphere cells mounted directly on normal glia migrated away through the glial fibrous scaffold and decelerated their differentiation, whereas it mounted on VPA-administered glia did not form fibrous morphology. Neuronal differentiation in GCM showed a decrease of synaptogenesis compared with it in normal differentiation medium, whereas, VPA-administered glia-conditioned differentiation medium (VPA-GCM) promoted a similar level of synaptogenesis with normal differentiation medium. Therefore, we suggest that some humoral factors in GCM would be related to neuronal differentiation and the candidate molecules might be secreted by microglia which is known as an immune cell in brain development. The sorts and quantity of those factors would be different between in GCM and VPA-GCM.

Disclosures: C. Nishikawa: None. **K. Sato:** None. **N. Hozumi:** None. **Y. Fueta:** None. **S. Ueno:** None. **Y. Sekino:** None. **Y. Kanda:** None. **Y. Nomura:** None. **S. Yoshida:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.13/V7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Ministry of Science, ICT&Future Planning (grant number 18-BR-02-04)
NRF 2016R1A2B4011393

Title: Epimedium koreanum Nakai inhibits PMA-induced cancer cell migration and invasion in malignant human glioma cells

Authors: *J. KIM[1], W. LEE[1], J. NAM[1], J.-Y. LEE[1], Y.-M. WE[2], J. MA[3], H.-S. HOE[1]
[1]Korea Brain Res. Inst., Daegu, Korea, Republic of; [2]Hyoo Med. Clin., Seoul, Korea, Republic of; [3]Korean Med. (KM)-Application Ctr., Daegu, Korea, Republic of

Abstract: Previously, we showed that the herbal extract EYK (*Epimedium koreanum* Nakai) can regulate the immune response. Other studies showed that EYK has beneficial effects in human lung cancer, angiogenesis, and Alzheimer's disease (AD). However, it remains unknown whether EYK can affect cancer cell migration and invasion in human brain cancer cell lines. In this study, we found that pre- or post-treatment with EYK inhibited phorbol 12-myristate 13-acetate (PMA)-induced cancer cell migration and invasion in A172 cells, but not in U373MG or T98G cells. Additionally, pre- or post-treatment with PMA followed by EYK decreased MMP-9 activity in A172 cells. Moreover, treatment with a NF-κB inhibitor significantly decreased cell migration in A172 cells pre- or post-treated with EYK and PMA, suggesting that EYK requires NF-κB to alter cancer cell migration. Either pre-or post-treatment with EYK significantly decreased NF-κB nuclear translocation in comparison with PMA treatment. Taken together, our results suggest that EYK suppresses PMA-induced cancer cell migration in monomorphic malignant human glioma cells by downregulating the NF-κB pathway and decreasing MMP-9 activity.

Disclosures: J. Kim: None. **W. Lee:** None. **J. Nam:** None. **J. Lee:** None. **Y. We:** None. **J. Ma:** None. **H. Hoe:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.14/V8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Institutes of Health
Oak Ridge Institute for Science Education

Title: Evaluation of the cyclin dependent kinase inhibitor cr8 to mitigate neuroinflammatory responses following cessation of nerve agent-induced seizures

Authors: *D. D. PALMER, C. E. KAROLENKO, N. GARIBAY, K. LAITAPAYA, B. LAGER, J. CHANDLER, E. A. JOHNSON, J. W. SKOVIRA
US Army Med. Res. Inst. of Chem. Def., Gunpowder, MD

Abstract: Organophosphate (OP) nerve agents cause excessive excitatory signaling in the central nervous system through mechanisms involving inhibition of cholinesterase. Persistent seizures are a result of excessive signaling and can lead to progressive brain damage. Although great focus has been placed on interventions to control OP-induced seizures, few studies have examined the pathological processes that continue after seizures have been abated. The objective of this study is to determine (1) whether cellular neuroinflammatory responses continue following cessation of OP-induced seizures and (2) whether the cyclin-dependent kinase (CDK) inhibitor CR8 can mitigate the extent of the neuroinflammatory response. Mice were surgically prepared two weeks prior to the experiment with electrodes to record brain activity. The oxime HI-6 (50mg/kg) was given prior to nerve agent exposure to increase survival without affecting the onset of seizure activity. Mice were exposed to the nerve agent sarin to elicit seizure activity (256 µg/kg; control animals received an equivalent volume of saline). The CDK inhibitor CR8 (5mg/kg, ip) was administered 5 min following seizure onset. Seizures were terminated with midazolam (5 mg/kg) and the centrally active oxime monoisonitrosoacetone (50 mg/kg) at 15, 30, or 60 min following onset. Brain tissue was collected at 7 d or 30 d following exposure for analysis of gliosis and neuronal survival. The results suggest that nerve agent casualties may still be at risk for progressive neurodegeneration from the continuation of inflammatory processes, even if seizures are successfully terminated. CR8 treatment significantly reduced the extent of neuroinflammatory responses, thus aiding in neuroprotection following OP-induced seizures.

Disclosures: D.D. Palmer: None. **C.E. Karolenko:** None. **N. Garibay:** None. **K. Laitapaya:** None. **B. Lager:** None. **J. Chandler:** None. **E.A. Johnson:** None. **J.W. Skovira:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.15/V9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: The serine protease tPA modulates the phosphorylation of mTOR and autophagy during ischemic events

Authors: *A. THIEBAUT, D. VIVIEN, B. D. ROUSSEL
INSERM U1237, Caen Cedex 5, France

Abstract: The serine protease tissue type plasminogen activator (tPA) is a glycoprotein involved in thrombolysis and also found in the neurovascular unit where it has both deleterious and protective effects. tPA is known to be involved in excitotoxicity, apoptosis and inflammation. More recently, it has been reported that tPA protects neurons from oxygen and glucose deprivation (OGD)-induced endoplasmic reticulum (ER) stress (Louessard *et al.,* Cell Death Differ 2017) by binding to cell surface Grp78 (78 kD glucose-regulated protein). It leads to a decrease of the PERK pathway activation and results in neuroprotection. Plus, it has been shown that mTOR (mammalian target of rapamycin) activation mediates the neuroprotective effect of tPA following OGD-induced neuronal death (Wu *et al.,* J Neurosci 2011). mTOR complex 1 (mTORC1) is known to negatively regulate the initiation of autophagy. Moreover, it is well-known that ER stress and autophagy are closely linked. Here, we study autophagy during OGD-induced ER stress, and the effect of tPA on these events. In this study we used an *in vitro* ischemic model consisting in an OGD followed by reoxygenation, on twelve days old murine primary cortical neurons with or without tPA. First, we studied autophagy in OGD and reported that OGD induces a decrease of the Erk/Akt/mTORC1 pathway leading to an increase of the Light Chain 3-I (LC3-I) conversion to LC3 II, a microtubule-associated protein involved in autophagosome formation. Moreover, we observed a decrease of p62, also called sequestosome 1, a cargo-receptor itself degraded by autophagy, able to link ubiquitinated protein to enable their degradation by the lysosome. In a second time, we investigated the effect of tPA on autophagy during OGD. We show that tPA can decrease the LC3I conversion to LC3 II and increases p62. tPA is able to decrease autophagosome formation *via* an activation of the Erk/Akt/mTORC1 pathway. In conclusion, the present study demonstrates that tPA decreases OGD-induced autophagy, by reducing autophagosome formation via the activation of the Erk/Akt/mTORC1 pathway. The next step is to identify the cellular and molecular pathways involved in OGD-induced ER stress and autophagy to propose a new therapeutic target during stroke.

Disclosures: A. Thiebaut: None. **D. Vivien:** None. **B.D. Roussel:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.16/V10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: MET activation modulates sctPA-mediated NMDA receptor signalling and neurotoxicity

Authors: E. HEDOU[1], A. THIEBAUT[1], A. CHEVILLEY[1], I. BARDOU[1], C. ALI[1], T. CREPALDI[2], P. COMOGLIO[2], D. VIVIEN[1,3], *B. D. ROUSSEL[1]
[1]INSERM U1237, Caen Cedex 5, France; [2]Candiolo Cancer Inst. IRCCS-FPO, Turin, Italy; [3]Dept. of Clin. Res., Caen Univ. Hosp., Caen, France

Abstract: Tissue type-plasminogen activator (tPA) is a serine protease used as a fibrinolytic agent to treat ischemic stroke. This protease is also expressed within the central nervous system where it is synthesized and released as a single-chain form (sc-tPA) and can be converted into a two-chain form (tc-tPA). Both of them have the same fibrinolytic activity but they display a differential effect on neuronal fate. Indeed, it has been described that sc-tPA is a positive neuromodulator of the glutamatergic transmission, inducing an overactivation of neuronal N-methyl-D-aspartate receptor (NMDAR) and a subsequent calcium influx . Under pathological conditions such as stroke, this phenomenon will enhance the excitotoxic neuronal death.. However, tc-tPA does not overactivate NMDAR, suggesting different mechanisms of action for the two forms of the same protease.
The aim of our study is to identify the mechanisms by which sc- and tc-tPA influence NMDAR signalling. tPA has been shown to be a pro-HGF convertase, capable to process the biologically inactive precursor into the mature form . As the main receptor for HGF is Met, we hypothesized that sc/tc-tPA could directly (though a binding to Met) or indirectly (by converting the pro-HGF into HGF) activate Met signalling and thus modulate NMDAR signalling.
Our data indicates that tPA is not able to convert pro-HGF into mature HGF. However the activation of MET receptor by HGF is able to decrease tPA-induced NMDAR signalling and the subsequent neurotoxicity, as demonstrated by Proximity Ligation Assay, live calcium imaging, toxicity experiments, and pharmacological approach.
Our results prove that MET receptor is able to modulate NMDAR signalling and decrease the associated toxicity, making of MET receptor a new therapeutic target to decrease excitotoxicity.

Disclosures: E. Hedou: None. **A. Thiebaut:** None. **A. Chevilley:** None. **I. Bardou:** None. **C. Ali:** None. **T. Crepaldi:** None. **P. Comoglio:** None. **D. Vivien:** None. **B.D. Roussel:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.17/V11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Fund for New Recruits (1-ZE5L)
University Resaerch Grant (G-YBR0)
University Resaerch Grant (G-YBWJ)
Health Medical Research Fund (15161201)

Title: Developing an animal model for studying cognitive impairment in chronic kidney disease

Authors: *J. Y.-S. HO[1], C. F. LAU[1], W. Y. TANG[3], J. Y. TIAN[2], R. YOU[2], C. C. C. PANG[2], D. S. K. CHEUNG[2], S. S. Y. YUNG[3], R. C. C. CHANG[3]
[1]Sch. of Nursing, [2]The Hong Kong Polytechnic Univ., Hong Kong, China; [3]The Univ. of Hong Kong, Hong Kong, China

Abstract: Cognitive impairment are common among patients with chronic kidney disease (CKD). There is also increased risk of developing dementia among CKD patients. The affected cognitive domains include attention, executive functions and memory. Cognitive impairment is associated with poor decision making, reduced self-care ability and increased risk of disability. Apart from protecting the kidney, preserving cognitive functions have become one of the major concerns in recent CKD research. Currently, the mechanism that links the disease kidney and the brain is still unclear. Our group has established a mouse model for studying cognitive impairment in CKD. Eight weeks old male C57BL/6 mice were anesthetized to perform the Unilateral Ureteral Obstruction (UUO) surgery. The left ureter was ligated with silk thread. Sham operated mice received the same experimental procedure without ureteral obstruction. Three months after the surgery, the mice were subjected to behavioral tests and pathological changes were detected in their frontal cortex. We found that the UUO group made significant increased number of error in in the modified Y-maze test when comparing to the sham group. They also had poorer performance in the novel object recognition (NOR) test. These suggested impairment in the hippocampal-dependent memory. In the Puzzle Box test, mice in the UUO group spent significant longer time to reach the dark zone, suggesting a reduction in executive function. At the same time, we found that the protein expression of synaptophysin was reduced, and the levels of phosphorylated tau were increased, and the levels of drebrin were reduced in the frontal cortex of the UUO group. Oxidative stress and inflammation were also found in the brain of the UUO mice. In conclusion, we were able to detect cognitive impairment in mice that had received UUO surgery. Related pathological changes in their brain including inflammation, synaptic dysfunction and changes in tau protein may partly explained the observed phenomenon.

These will be useful for our future investigation on developing new intervention for preserving cognition.

Disclosures: J.Y. Ho: None. **C.F. Lau:** None. **W.Y. Tang:** None. **J.Y. Tian:** None. **R. You:** None. **C.C.C. Pang:** None. **D.S.K. Cheung:** None. **S.S.Y. Yung:** None. **R.C.C. Chang:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.18/V12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Autphagy induction in brain by severe hypoglycemia and its modulation by the ketone bodybeta-hydroxybutirate

Authors: *M. TORRES ESQUIVEL[1], M. FLORES-MÉNDEZ[2], T. MONTIEL[2], L. MASSIEU[2]
[1]Univ. Nacional Autonoma De México, CDMX, Mexico; [2]Inst. de Fisiología Celular, Univ. Nacional Autonoma de México, Cdmx, Mexico

Abstract: During hypoglycemia alternative substrates to glucose such as the ketone bodies (KB), acetoacetate (AcAc) and β-hydroxybutyrate (BHB) can be used as energy in brain. Furthermore diverse studies have shown that KB prevent neuronal death in different injury models. Nevertheless, the mechanisms by which KB prevent neuronal damage are still not well understood. Previous studies from our group have suggested that autophagy, a lisosomal-dependent degradation process activated during energy failure, participates in neuronal death induced by glucose deprivation in cultured cortical neurons. In these conditions, D-BHB, stimulates the autophagic flux and prevents neuronal death (J.Neurosci.Res. 41:600). In the present study we aimed to investigate whether autophagy is activated in vivo during insulin-induced hypoglycemia and glucose reperfusion and whether the neuroprotective effect of D-BHB, is related to autophagy. We analyzed the changes in the content of the autophagy proteins, LC3-II, used as index of autophagosome formation, and p62/SQSTM1, involved in autophagic degradation by western blot, in the cortex and hippocampus of hypoglycemic rats treated or not with BHB. Results show that autophagosome accumulation is promoted after 2 h of severe hypoglycemia in all studied cerebral regions as evidenced by the increased levels. 6 h after glucose reperfusion LC3-II content decreased to basal levels, suggesting less autophagosome formation or stimulated autophagosome degradation. However, after 24 h a second increase in LC3-II was observed in rats exposed to the hypoglycemic coma, while in those treated with D-BHB a significant decrease in LC3-II content was observed, suggesting that less autophagosomes are formed. No changes in p62/SQSTM1 were observed in the cortex, while in the hippocampus, a significant decrease in p62/SQSTM1 content was observed at 24 h in

animals treated with D-BHB, suggesting the stimulation of the autophagic flux. Altogether these results suggests that D-BHB prevent autophagosome formation and stimulates the autophagic flux during in vivo hypoglycemia.
This work was supported by CONACYT CB-239607 grant to L. M

Disclosures: M. Torres Esquivel: None. **M. Flores-Méndez:** None. **T. Montiel:** None. **L. Massieu:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.19/V13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Start-up funds to Dr. Spencer
UT Brain Initiative
BBRC

Title: A novel neuroinvasive infection modality for francisella tularensis elicits neuroinflammation resulting in cellular damage

Authors: *M. G. RAMOS MUNIZ[1], R. CONTRERAS[2], A. TENA[2], C. T. SPENCER[2]
[2]Biol. Sci., [1]Univ. of Texas at El Paso, El Paso, TX

Abstract: *Francisella tularensis* (*Ft.*) is a gram-negative coccobacillus bacterium that causes the zoonotic disease tularemia in humans. *Ft.* causes the most severe, and fatal form of the disease through inhalation, however, *Ft.* is most commonly transmitted through direct contact with infected animal carcasses such as rodents and rabbits, consumption of contaminated food or water, and through arthropod bites, particularly ticks. Due to the extremely low infectious dose and high mortality rate, along with its potential use as a biological warfare agent, *Ft.* is classified by the CDC as a Tier 1 select agent. *Ft.* infection triggers an overactive inflammatory response, termed a cytokine storm, which often results in excessive tissue damage of vital organs causing multiple organ failure, therefore, leading to rapid death of the host before onset of adaptive immunity. In the periphery, macrophages, paradoxically the target cell for *Ft.*, provide innate immune defense against foreign material, including bacteria. Microglial cells, the resident macrophages of the brain and spinal cord, have been reported to rapidly respond to pathological changes in the central nervous system, serving a similar function as macrophages. Their rapid activation is an important factor in guarding the neural parenchyma against infectious diseases, inflammation, and neurodegeneration while maintaining and facilitating the return to tissue homeostasis. We made the novel observation that following peripheral infection the bacterium is trafficked to the brain. The purpose of this project is to identify the consequences of neuronal

infection after peripheral inoculation with *Ft.*. Since in the periphery, macrophages are the target cell for *Ft.*, it is likely that microglia cells may be the cell target in the brain. We hypothesize that after peripheral inoculation of *Ft.*, the bacteria then infiltrate the central nervous system using a Trojan horse-type mechanism allowing for infection of microglia cells, leading to overproduction of pro-inflammatory cytokines in the brain which then cause damage to surrounding neuronal cells ultimately leading to death. The proposed specific aims of this project are to 1) identify the cellular targets of *Ft.* in the central nervous system, 2) determine the resulting level of cytokine production from infected microglial cells, 3) identify the immune cell subsets in the brain that are activated after CNS infection, and 4) identify the mechanism being used by *Ft.* to infiltrate the central nervous system.

Disclosures: M.G. Ramos Muniz: None. **R. Contreras:** None. **A. Tena:** None. **C.T. Spencer:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.20/V14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01CA194924

Title: Mammary tumor and mastectomy synergistically promote chronic neuroinflammation in a breast cancer survivor model

Authors: *K. EMMER[1], W. H. WALKER, II[1,2], N. ZHANG[2], A. C. DEVRIES[2]
[1]The Ohio State Univ., Columbus, OH; [2]West Virginia Univ., Morgantown, WV

Abstract: Even after treatment for breast cancer ends, many women experience mental sequelae including depression and anxiety that can last for years. Understanding the cause of these cognitive deficits is essential for developing targeted treatment plans and improving quality of life for breast cancer survivors. Microglial priming results in heightened responses to homeostatic disturbances thereby exacerbating neuroinflammation and neurodegeneration, and offers a potential mechanism for this cognitive dysfunction. This study examined whether mammary gland tumors prime microglia and augment the inflammatory profile and behavior of mice. To test this, we injected non-metastatic mammary tumor cells (67NR) orthotopically into BALB/c mice, allowed them to grow for 16 days, and then removed the tumors via mastectomy. Following 14 days of surgical recovery, we challenged the mice with lipopolysaccharide (LPS), then evaluated central and peripheral inflammation, anxiety, and depressive-like behavior. Here we show that after 16 days of tumor growth (the time of mastectomy surgery), there were no significant differences in inflammatory markers in the hippocampus or serum apart from

increased serum CXCL1 concentrations in tumor-bearing compared to non-tumor-bearing animals. Similarly, mastectomy surgery alone did not significantly affect major central or peripheral inflammatory markers. Interestingly, hippocampal mRNA expression of proinflammatory cytokines IL-1β and TNFα along with microglial scavenger receptor CD68 was increased following surgical recovery in mastectomy tumor removal animals relative to control animals. Nonetheless, after LPS administration there were no exaggerated immune responses or behavioral changes to substantiate microglial priming in the tumor removal group. In sum, these data demonstrate that tumor-bearing together with mastectomy surgery promotes neuroinflammation and microglial activation; however, immune challenge with LPS did not elucidate this inflammation as maladaptive for the host.

Disclosures: K. Emmer: None. **W.H. Walker:** None. **N. Zhang:** None. **A.C. DeVries:** None.

Poster

659. Neurotoxicity, Inflammation, and Neurodegeneration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 659.21/V15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Transcriptome of the mice hippocampus differently affected after subarachnoid hemorrhage (SAH)

Authors: *A. S. REGNIER-GOLANOV[1], L. PETERSON[3], E. I. BOVSHIK[2], E. V. GOLANOV[2], G. W. BRITZ[1]
[2]Neurosurg., [1]Houston Methodist Hosp., Houston, TX; [3]Ctr. for Outcome Res., Houston Methodist Res. Inst., Houston, TX

Abstract: SAH survivors present long-term neurological aberrations with signs of depression, anxiety and cognitive impairment. These disabilities are sufficiently significant that 44% of the SAH patients are unable to continue with their professional activities. SAH is often followed by general brain atrophy including the temporomesial area. The latter correlates with neurocognitive disorders. These observations are suggestive of hippocampal abnormalities following SAH. While hippocampal abnormalities have been demonstrated in acute period following the hemorrhage, the underlying molecular and cellular mechanisms of cognitive outcome after the initial ictus are still not completely understood. To identify leading processes in the hippocampus following SAH we used RNA next-generation sequencing to explore the changes in gene expression at the transcriptional level 4-days after SAH. SAH was induced in anesthetized male C56BL/6J mice (10 to 14-weeks old) by monofilament perforation of the circle of Willis. In sham-operated mice the filament was advanced to the perforation point and withdrawn without puncture. RNA of the whole hippocampus of SAH (n=4), sham (n=3) and naïve (n=3) group was extracted using Quiazol, and only RNA with RIN>9.0 were further sequenced. Reads alignment

(20-30.10^6/samples), fragments count and differential expression gene (DEG) analysis were done using Partek Genomic Suite 7.0. In total 20,067 genes were identified. Differential expression analysis showed 449 genes significantly differ between SAH and sham (-1.5<fold change>1.5; $p<0.05$) with 74% specific to SAH, and 142 genes were significantly changed between sham and naïve. About 6.9% of DEGs in SAH and sham overlapped suggesting that these genes relate to the surgery procedure. Gene ontology and pathway analysis (DAVID 6.8) showed that DEGs were prevalent in the categories of immune processes, angiogenesis, antigen processing and presentation, and extracellular matrix (false discovery rate [FDR]<10^{-4}). Gene set enrichment analysis with all genes sequenced (GSEA, FDR <0.15) revealed enrichment in complement, astroglial phenotype, interferon gamma and alpha, and depletion in oligodendrocytic phenotype. Prevalent transcriptome changes in the hippocampus in the subacute period (4 days) suggest that processes related to inflammatory and defense responses mostly localized to the extracellular domain are dominant in the hippocampus following the hemorrhage.

Disclosures: A.S. Regnier-Golanov: None. **L. Peterson:** None. **E.I. Bovshik:** None. **E.V. Golanov:** None. **G.W. Britz:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.01/V16

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2017R1A2B4009478

Title: Inflammation and CX3CR1 are involved in pathology of pain-mediated cognitive/emotional dysfunction after orthopedic surgery in mice

Authors: *S. KIM[1], B. KOO[2]
[1]Dept. of Anesthesiol. and Pain Med., Seoul, Korea, Republic of; [2]Dept. of Anesthesiol. and Pain Med., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Background Post-operative pain is common complication after surgery and closely associated with postoperative cognitive dysfunction. The previous studies suggested regulation of neuro-immune interactions is important during neuropathic pain and CX3C chemokine receptor 1 (CX3CR1) plays a key role in pain and inflammation. Therefore, in this study, we performed orthopedic surgery and confirmed CX3CR1 and inflammatory mediator levels in the spine and brain regions. **Materials and Methods** We used a model of tibial fracture with intramedullary pinning in ICR male mice. After surgery, we assessed pain behavioral test (von frey filaments), and cognitive/anxiety tests (passive avoidance test, open field test, novel

objective recognition test, elevated plus maze). At different time points, we confirmed the levels of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and Tumor necrosis factor alpha (TNF-α) in the lumbar spine, hippocampus, amygdala, and prefrontal cortex. The level of CX3CR1 was also measured in same regions after tibial fracture with pinning. **Results** In our data, mice showed mechanical allodynia at 1, 2, and 5 days after tibial fracture. Learning and memory were impaired after tibial fracture: in passive avoidance test, latency time to enter the dark compartment was significantly reduced at 5 days after tibial fracture, compared to the control. In novel objective recognition test, mice were showed reduced exploration time of new objects at 1, 2, and 5 days after tibial fracture, compared to the baseline, and in elevated plus maze, mice were exhibited lower learning index at 1, 2, and 5 days after tibial fracture, compared to the control. Anxiety-related behavior was increased after tibial fracture: in open field test, mice were showed reduced distance and time of central zone at 1, 2, and 5 days after tibial fracture, compared to the control and in elevated plus maze, time to enter closed arm was increased at 1 and 2 days in tibial fracture group, compared to the control group. By the enzyme-linked immunosorbent assay, IL-1β, IL-6 and TNF-α protein levels were upregulated at different time point after tibial fracture and *Cx3cr1* transcrips were upregulated at 2 days after tibial fracture. **Conclusions** We proved that tibial fracture surgery triggered proinflammatory cytokines and CX3CR1 expressoin in the lumbar spine and brain regions. Also, this surgery induced abnormal pain hypersensitivity and cognitive/emotional dysfunction. It is likely that inflammation and CX3CR1 is mainly involved in pathology of pain-mediated cognitive/emotional dysfunction after orthopedic surgery.

Disclosures: S. Kim: None. **B. Koo:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.02/W1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CIHR Grant MOP-11246

Title: Glycolysis drives leukocyte migration and subsequent neuropathology in an animal model of multiple sclerosis

Authors: *D. K. KAUSHIK[1], A. BHATTACHARYA[2], C. SILVA[2], V. WEE YONG[2]
[2]Clin. Neurosciences, [1]Univ. of Calgary, Calgary, AB, Canada

Abstract: The transmigration of leukocytes into the central nervous system (CNS) is a defining feature of multiple sclerosis (MS). Leukocytes penetrate into the CNS via several routes

including across the post-capillary venules where they accumulate initially in the perivascular space forming structures referred to as perivascular cuffs. The migration of leukocytes into the CNS across the blood brain barrier (BBB) likely utilizes significant energy resources that remain to be defined. Using the inflammatory mouse model of MS, experimental autoimmune encephalomyelitis (EAE), we found that leukocytes that remain within the perivascular space express the inducible glycolytic enzyme lactate dehydrogenase A (LDHA) that converts pyruvate to lactate. The lactate generated intracellularly is normally shuttled out via specialized transporters known as the monocarboxylate transporters (MCTs), and MCT-4 is known to efficiently accomplish this role in glycolytic cells. Accordingly, we found that leukocytes within inflammatory perivascular cuffs in cerebellum and spinal cords were strongly immuno-reactive for MCT-4 at peak clinical severity of EAE. The expression of MCT-4 on leukocyte membranes was regulated by extracellular matrix metalloproteinase inducer (EMMPRIN, CD147) as determined through co-expression studies, silencing, and by co-immunoprecipitation. Functional importance of glycolysis and MCT-4 in the infiltrating leukocytes was demonstrated by significant reduction of macrophage transmigration in culture following exposure to the selective LDHA inhibitor FX11, and to the MCT-4 inhibitor, the cinnamon derivative α-cyano 4-hydroxy-cinnamic acid (CHCA). Further, EAE mice treated with CHCA formed fewer cuffs in the spinal cords and exhibited significantly reduced clinical severity and histopathology as compared to the PBS-treated sham group. These results were mirrored by strong expression of MCT-4 and LDHA in inflammatory perivascular cuffs in brains from patients with MS. Our results suggest that glycolysis plays a crucial role in conferring the infiltrating leukocytes a pro-inflammatory phenotype and identify CHCA as a potential modulator of neuroinflammation in MS with therapeutic and dietary implications.

Disclosures: D.K. Kaushik: None. **A. Bhattacharya:** None. **C. Silva:** None. **V. Wee Yong:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.03/W2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Treatment with a CCR3 antagonist rescues neuroinflammation and cognitive dysfunction in acute and chronic LPS models

Authors: *S. REGE, H. HACKBART, E. CZIRR, S. P. BRAITHWAITE, S. S. MINAMI
Alkahest, Inc., San Carlos, CA

Abstract: Peripheral inflammation has been associated with cognitive dysfunction in both animal models and humans. Elevated levels of systemically circulating cytokines, a hallmark of inflammation, have been shown to correlate with lower cognitive performance. Further, the correlation between cognitive dysfunction and chronic peripheral inflammation in patients with type 2 diabetes or Alzheimer's disease has been well established. We, and others, have identified that eotaxin is a cytokine that is elevated peripherally in plasma in aging and disease and induces deficits in cognitive function.
Here we demonstrate that an antagonist of CCR3, the primary receptor of eotaxin, is efficacious in both acute and chronic models of LPS treatment in 2-month old C57BL/6 mice. A single dose of LPS (5mg/kg) was administered in the acute model, with cognitive dysfunction and neuroinflammation presenting one month later. These mice were treated with the CCR3 antagonist for 4 weeks following LPS injection and showed significantly reduced microglial activation in the hippocampus. Daily doses of LPS (0.5mg/kg) for 7 weeks were administered in the chronic model with treatment with the CCR3 antagonist for the last 4 weeks. In this chronic LPS model there was reduced neuroinflammation in the brain as well as reduced cognitive dysfunction after compound treatment. Our findings demonstrate that targeting the CCR3 receptor with an antagonist has therapeutic potential to alleviate CNS deficits associated with peripheral inflammation.

Disclosures: S. Rege: A. Employment/Salary (full or part-time):; Alkahest, Inc. **H. Hackbart:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **E. Czirr:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **S.P. Braithwaite:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **S.S. Minami:** A. Employment/Salary (full or part-time):; Alkahest, Inc..

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.04/W3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Translational PET imaging of neuroinflammation in pre-clinical rodent models of neurogenerative diseases

Authors: *J. RYTKÖNEN[1], P. POUTIAINEN[2], D. MISZCZUK[1], A. J. NURMI[1], T. HUHTALA[1]
[1]Charles River Discovery, Kuopio, Finland; [2]Kuopio Univ. Hosp., Kuopio, Finland

Abstract: Pre-clinical nuclear imaging provides a translational approach to monitor progression of inflammation can be applied in several rodent models with neuroinflammation. Neuroinflammation is associated with several neurodegenerative diseases, including multiple

sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, and stroke. Mitochondrial translocator protein (TSPO) activation and changes in metabolic activity have been associated with neuroinflammation in central nervous system. Therefore TSPO ligands, glucose and acetate analogues, radiolabelled with positron emitting isotopes, can be applied to image the progression of neuroniflammation *in vivo*. TSPO expression in the brain is associated with activation of microglia, therefore TSPO is potential target to evaluate neuroinflammatory changes in a variety of CNS disorders. However, there is always a baseline expression present which prohibits the use of reference tissue models in dynamic PET imaging. To reach optimal readouts from the imaging and understand PET tracer kinetics metabolite corrected arterial input function has to be collected from the imaged animal. Optionally static PET imaging can be applied but static PET imaging data is more prone for variation due to technical aspects and data interpretation has to be made carefully.
Neuroinflammation was studied with TSPO PET and metabolic changes with FDG PET in several animal rodent models of neurodegenerative diseases. Furthermore, neuroinflammatory markers, including immunohistochemistry (IHC), were used as supportive readout. *In vivo* imaging TSPO PET imaging was used to effectively monitor neuroinflammation. Additionally, the metabolic alterations associated with neuroinflammation could be quantified with FDG PET imaging. IHC data provided supportive indications for the models.
As a summary, PET imaging gives multiple options to study neuroinflammation in pre-clinical for CNS disease animal models. It is a powerful research tool allowing comprehensive evaluation of disease progression and treatment interventions in vivo studies.

Disclosures: J. Rytkönen: None. **P. Poutiainen:** None. **D. Miszczuk:** None. **A.J. Nurmi:** None. **T. Huhtala:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.05/W4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Pathological hallmarks of a genetic and an induced Gaucher disease mouse model

Authors: *J. NEDDENS, E. SANTIAGO-MUGICA, S. FLUNKERT, V. NIEDERKOFLER, R. RABL, D. AMSCHL, M. POSCH, E. AUER, B. HUTTER-PAIER
Neuropharm., QPS Austria GmbH, Grambach, Austria

Abstract: Introduction: 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 β-glucosidase (GCase) with a point mutation at V394L/V394L. Additionally, the disease can be modeled by treating mice with Conduritol-beta-Epoxide (CBE) a specific inhibitor of GCase activity.
To use these models for compound tests against the Gaucher disease a detailed characterization of these mice is needed. We thus analyzed 4L/PS-NA mice for their neurono- and non-neuronopathic features and treated wildtype mice for 15 days daily intraperitoneally with 100 mg/kg CBE.
Method: Both mouse models were analyzed for behavioral symptoms. Furthermore brain tissue of both models was analyzed for Gaucher disease relevant pathologies by histological methods. The 4L/PS-NA mouse model was further analyzed for visceral symptoms.
Results: Our results show that both mouse models present neuroinflammation by glial activation. Furthermore, 4L/PS-NA mice display a progressive muscle strength and motor coordination deficit, while CBE treated animals show no relevant motor deficits. Visceral organs like spleen, thymus, lung and liver of 4L/PS-NA mice are characterized by enlarged leukocytes and macrophages that are already visible at early age.
Conclusion/ Summary: In summary, 4L/PS-NA mice present with highly increased glial activation in the brain that is accompanied by strong motor deficits suggesting that 4L/PS-NA mice are a good model to study the chronic neuronopathic type 3 Gaucher disease in humans. Additionally, 4L/PS-NA mice present early alterations in visceral organs and thus further mimicking the non-neuronopathic phenotype of Gaucher disease. Treatment with CBE causes no motor deficits but strong neuroinflammation, suggesting that this induced model has in total a weaker phenotype compared to the 4L/PS-NA model.

Disclosures: J. Neddens: None. **E. Santiago-Mugica:** None. **S. Flunkert:** None. **V. Niederkofler:** None. **R. Rabl:** None. **D. Amschl:** None. **M. Posch:** None. **E. Auer:** None. **B. Hutter-Paier:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.06/W5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: PEALut treatment: Role in preclinical and clinical delirium manifestations

Authors: *R. CRUPI, R. SIRACUSA[1], M. CORDARO[1], D. IMPELLIZZERI[1], A. PERITORE[1], R. DI PAOLA[1], S. CUZZOCREA[1,2]

[1]Biol. and Envrn. Sci., Univ. of Messina, Messina, Italy; [2]St. Louis Univ. Sch. of Med., Saint Louis, MA

Abstract: Delirium is a disturbance in attention, awareness and cognition. It is an aberrant response to stress that produces a syndrome of physiological and behavioral changes termed "sickness behaviour". Postoperative delirium (POD) is a common complication in elderly patients after hip fracture surgery and usually occurs within 5 days after surgery, especially during the first 24-48 h postoperatively. Neuroinflammation, is an important etiological factor associated with the development of POD. The lipopolysaccharide injection in mice has potency for performing mechanistic studies important to understanding how systemic inflammation and underlying neurodegeneration interact to induce delirium. Actually, there are no licensed treatments to manage delirium but it was recognized an interest in a role of the endocannabinoid system in neuropsychiatric disorders. N-Palmitoylethanolamine (PEA) acts as a lipid signaling molecule with antiinflammatory activity in preclinical models of acute and inflammatory pain and central nervous system injury and is efficacious for pain relief in man; Luteolin (Lut), a flavone of vegetable origin, is able to exert an antioxidant action. In our preclinical part of the study we focused on the hippocampus because it is sensitive to the insults of inflammation and is presumable involved in acute cognitive disorders that are relevant in patients with systemic infections.
Preclinical data demonstrate that co-ultraPEALut ameliorate cognitive function, emotional alteration and locomotor activity; moreover reduce the release of excitotoxic mediators, inflammation and apoptosis; stimulate anti-oxidant response and limite the loss of neurotrophins. In the second part of the research we studied the effects of co-ultraPEALut (Glialia®) administration in elderly hip fractured patient with an interventional, spontaneous, randomized, single-blind, monocentric study. The results obtained from the clinical study demonstrate that administration of co-ultraPEALut in elderly surgical patients with hip fracture is able to prevent the onset of POD and to attenuate the intensity of the symptoms and duration.

Disclosures: R. Crupi: None. **R. Siracusa:** None. **M. Cordaro:** None. **D. Impellizzeri:** None. **A. Peritore:** None. **R. Di Paola:** None. **S. Cuzzocrea:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.07/W6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NIH/NINDS R01NS080844

Newborn Medicine Funds from the Department of Pediatrics, University of Mississippi Medical Center

Title: Systemic interleukin-1 receptor antagonist reduces hippocampal injury and improves cognitive deficits in juvenile rats following neonatal exposure to lipopolysaccharide

Authors: *L.-W. FAN[1], L.-T. TIEN[3], J. W. LEE[1], S. LU[1], C. P. TALATI[1], N. B. OJEDA[1], X. DAI[2], M. A. TUCCI[2], A. J. BHATT[1], R. D. SAVICH[1], Y. PANG[1]
[1]Pediatrics/Newborn Med., [2]Dept. of Anesthesiol., Univ. of Mississippi Med. Ctr., Jackson, MS; [3]Sch. of Med., Fu Jen Catholic Univ., New Taipei City, Taiwan

Abstract: Perinatal infection/inflammation is associated with cognitive deficits later in life. Our previous studies have shown that systemic administration of interleukin-1 receptor antagonist (IL-1ra) can protect against lipopolysaccharide (LPS)-induced brain inflammation and neurobehavioral dysfunction in neonatal rats. The objective of this current study is to further determine whether systemic IL-1ra-mediated neuroprotection protects against systemic LPS-induced chronic brain inflammation, hippocampal injury, and cognitive dysfunction in juvenile rats. Intraperitoneal (i.p.) injections of LPS (2 mg/kg) or saline were performed in postnatal day 5 (P5) Sprague-Dawley rat pups of both sexes (equal numbers of males and females), and IL-1ra (100 mg/kg) or vehicle was administered (i.p.) at 5 min and 24 h after LPS injection. One animal from each sex from each litter was included in each experimental group. Four groups of 8 pups per group were include in the present study: Saline+Vehicle, Saline+IL-1ra, LPS+Vehicle, and LPS+IL-1ra. The control rats were injected with saline followed by vehicle (saline+0.1% BSA) in rats (Saline+Vehicle). Neurobehavioral tests were carried out from P20 to P21, and brain injury was examined at P21 in a double-blind manner. To ensure scientific rigor the molecular assays and histological assessment were evaluated by triplicate, and the sample size were calculated to reach a statistical power of at least 0.85 for a $P<0.05$. Control animals were from the same strain and same vendor. Data were analyzed by two-way ANOVA followed by the Student-Newman-Keuls test. Our results showed that neonatal systemic LPS exposure resulted in cognitive deficits, as demonstrated by poor performance in Y-maze, Novel object recognition, and Passive avoidance tests. LPS treatment also led to chronic neuroinflammation and hippocampal neuronal injury, as indicated by loss of NeuN (a marker for neurons) immunoreactivity in the hippocampus of the P21 rat brain. Systemic IL-1ra treatment significantly attenuated LPS-induced cognitive deficits and hippocampal injury, which was associated with a significant reduction in the numbers of Iba1+ cells (microglia) and IL-1β concentration in the hippocampus of the P21 rat brain. No significant difference was observed between the male and female rats within the same treatment group. These results suggest that systemic IL-1ra provides protection against neonatal inflammation exposure-induced long-term cognitive impairments in juvenile rats, which may be associated with the blockade of LPS-induced pro-inflammatory cytokine IL-1β.

Disclosures: L. Fan: None. **L. Tien:** None. **J.W. Lee:** None. **S. Lu:** None. **C.P. Talati:** None. **N.B. Ojeda:** None. **X. Dai:** None. **M.A. Tucci:** None. **A.J. Bhatt:** None. **R.D. Savich:** None. **Y. Pang:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.08/W7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Pregabalin exerts a direct neuroprotective effect in an animal model of multiple sclerosis

Authors: *J. FERNANDEZ ORTH[1], P. HUNDEHEGE[1], P. ROEMER[1], T. MUENTEFERING[1], S. EICHLER[1], L. EPPING[1], S. ALBRECHT[1], F. ZIPP[2], M. CERINA[4], A. MENKE[1], K. BIRKNER[2], R. GOLLAN[2], K. GOEBEL[1], T. RUCK[1], H. WIENDL[1], A. GORJI[5], S. BITTNER[3], S. G. MEUTH[1]
[1]Inst. for Translational Neurol., Muenster, Germany; [2]Neurol. Clin., Mainz, Germany; [3]Neurol. Clin., Neurology Clinic, Germany; [4]Inst. for Translational Neurologyf, Muenster, Germany; [5]Dept. of Neurol. and Dept. of Neurosurg., Muenster, Germany

Abstract: Multiple sclerosis (MS) is a severe and chronic autoimmune disorder of the central nervous system (CNS), that represents the main cause of neurological disability in young adults from the Western world. Although central aspects of the MS pathophysiology have been already characterized, the cause of the disease is still unknown. Pregabalin (Lyrica®) is used in the treatment of central neuropathic pain in MS. Chemically, pregabalin is an analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), that instead of binding to GABA receptors, binds to the α2δ subunit of voltage-gated calcium channels (VGCCs). Consequently, pregabalin decreases the calcium influx and reduces the presynaptic neurotransmitter release. Due to its direct effect on neuronal calcium levels, we here hypothesized that pregabalin exerts a neuroprotective effect in in an animal model of MS (experimental autoimmune encephalomyelitis, EAE). We observed that both prophylactic and therapeutic pregabalin treatments during the EAE course significantly ameliorated the clinical symptoms and reduced immune cell infiltration into the CNS. However, ex vivo analyses of immune cells from EAE mice revealed no functional differences in terms of cytokine production and proliferation. Additionally, pregabalin did not have any effect on the activation and integrity of a primary endothelial cell layer modelling the blood brain barrier (BBB). Importantly, pregabalin had a direct impact on neurons as its application to hippocampal brain slices was able to reduce long-term potentiation. Furthermore, it decreased the inflammation-induced elevation of neuronal intracellular calcium levels in EAE lesions. We conclude that pregabalin exerts a neuroprotective effect in mice. Future studies need to show whether pregabalin might be used as direct neuroprotective MS therapeutic at early disease stages.

Disclosures: J. Fernandez Orth: None. **P. Hundehege:** None. **P. Roemer:** None. **T. Muentefering:** None. **S. Eichler:** None. **L. Epping:** None. **S. Albrecht:** None. **F. Zipp:** None. **M. Cerina:** None. **A. Menke:** None. **K. Birkner:** None. **R. Gollan:** None. **K. Goebel:** None. **T. Ruck:** None. **H. Wiendl:** None. **A. Gorji:** None. **S. Bittner:** None. **S.G. Meuth:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.09/W8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Sex-specific effects of central immune activation on memory consolidation

Authors: *C. K. POSILLICO[1], R. E. GARCIA-HERNANDEZ[2], N. C. TRONSON[1]
[1]Psychology, [2]Univ. of Michigan, Ann Arbor, MI

Abstract: The neuroimmune system is required for normal neural processes including learning and memory. Acute activation of the immune system has been shown to alter memory capabilities and memory-related signaling mechanisms, and persistent immune dysregulation may be both a cause and consequence of disorders of memory such as Alzheimer's disease and post-traumatic stress disorder (PTSD) which both correlate with altered immune function. Importantly, women are more likely than men to develop both Alzheimer's disease and PTSD, and underlying sex differences in immune function may be a contributing factor. We have previously demonstrated sex differences in hippocampal cytokine signaling following a peripheral immune challenge. Given these data, in this project we examined whether neuroimmune activation has differential effects on memory processes in both males and females. We used intracerebroventricular (ICV) administration of an immunostimulant and determined subsequent memory deficits and changes in memory-related signaling in male and female C57Bl/6 mice. Polyinosinic:polycytadylic acid (poly I:C) is a viral mimic consisting of synthetic, double-stranded RNA that stimulates toll-like receptor (TLR) 3 expressed on astrocytes, microglia, and neurons in the brain. We demonstrated that poly I:C 4 hours prior to contextual fear conditioning caused deficits in context fear memory at test three days later. Importantly, this disruption of memory was observed in female mice, but not in males, indicating that neuroimmune activation has sex-specific effects on memory. To further examine the effects of poly I:C on cellular activation during memory consolidation, we determined changes in hippocampal and amygdalar Arc and cFos activity after fear conditioning as a function of poly I:C treatment. To examine the effects of poly I:C on social memory, we used a social recognition memory task in which females interacted with a novel, same-sex conspecific. ICV infusions of

poly I:C immediately after this training session prevented females from recognizing a familiar mouse 24 hours later. Taken together, these data demonstrate that poly I:C administration differentially impacts memory mechanisms in females and in males, where females are more sensitive to the memory-impairing effects of neuroimmune activation. Uncovering the underlying mechanisms of immune disruption of memory processes in both sexes may help to explain the sex bias in memory-related disease prevalence and provide better directions for treatment development for both sexes.

Disclosures: C.K. Posillico: None. **R.E. Garcia-Hernandez:** None. **N.C. Tronson:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.10/W9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: FAPESP 2015/12152-2
FAPESP 2017/11213-6

Title: Sepsis-induced antinociception is associated with neuroinflammation and glial activation

Authors: *L. ANGENENDT DA COSTA, R. A. CAZUZA, N. N. SANTOS-JUNIOR, C. R. CATALÃO, J. M. G. TESSARI, M. J. A. ROCHA, C. R. A. LEITE-PANISSI
Univ. of São Paulo, Ribeirao Preto, Brazil

Abstract: Sepsis, a dysregulated host response to infection, can affect the central nervous system and lead to autonomic, cognitive and behavioral alterations. However, sensory evaluation during sepsis and the central mechanisms underlying this process are poorly investigated. Using male Wistar rats, we induced sepsis by cecal ligation and puncture (CLP) and after 24 hours the animals were submitted to different nociceptive tests (tail flick, acetone and von Frey). Periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) were punched out for cytokines and western blot analyses. A last group was used for glial morphology investigation by immunofluorescence. Septic animals showed reduced thermal and mechanical allodynia as well as increased thermal analgesia. This reduction in nociception could not be attributed to lethargy or a decrease in animal mobility, since we did not observe any alteration in the crossing and rearing number. Quantification of inflammatory mediators in PAG and RVM indicated increased IL-1β, IL-6 and TNF-α levels, which was associated with microglial and astrocyte activation in both nuclei. A reduction in BCL-2, an anti-apoptotic protein, indicates that cells in these brain areas are more vulnerable to death. We conclude that experimental sepsis reduces nociception

and it is associated with glial activation and neuroinflammation in brain regions associated with nociceptive modulation.

Disclosures: L. Angenendt Da Costa: None. **R.A. Cazuza:** None. **N.N. Santos-Junior:** None. **C.R. Catalão:** None. **J.M.G. Tessari:** None. **M.J.A. Rocha:** None. **C.R.A. Leite-Panissi:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.11/W10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant NIH/NINDS NS080844
Newborn Medicine Funds from the Department of Pediatrics, University of Mississippi Medical Center
104-CGH-FJU-06, Taiwan
MOST103-2320-B-030-005-MY3, Taiwan

Title: Systemic lipopolysaccharide induced spinal inflammation associated allodynia and hyperalgesia were reduced by minocycline in neonatal rats

Authors: *L.-T. TIEN[1], Y.-J. LEE[1], L.-W. FAN[2]
[1]Fu Jen Catholic Univ., Taipei, Taiwan; [2]Pediatrics/Newborn Med., Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: In this study, we investigated the effects of minocycline, a putative suppressor of microglial activation, on reducing systemic LPS-induced spinal cord inflammation, allodynia and hyperalgesia in neonatal rats. Intraperitoneal (i.p.) injection of LPS (2 mg/kg) or sterile saline was performed in P5 rat pups both sexes (equal numbers of males and females) and minocycline (45 mg/kg) or vehicle (PBS) was administered (i.p.) 5 min after LPS injection. The von Frey filament and tail-flick tests were performed to determine mechanical allodynia (decreased reaction thresholds to painful stimuli) and thermal hyperalgesia (decreased reaction latency to painful stimuli), respectively, and spinal cord inflammation was examined on P6. The results were analyzed by two-way ANOVA followed by the Student-Newman-Keuls test and results with a $p < 0.05$ were considered statistically significant. Systemic LPS administration resulted in reduction of tactile threshold in the von Frey filament tests and pain response latency in the tail flick test of P6 rats. LPS administration also significantly increased the levels of microglia and astrocyte activation, microglia-related pro-inflammatory cytokines including interleukin-1β (IL-1β), cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE2) in the P6 spinal cord. Treatment

with minocycline significantly attenuated the LPS-induced allodynia, hyperalgesia, and the increase of spinal cord microglia, astrocytes, and pro-inflammatory cytokine levels in P6 rats. No significant difference was observed between the male and female rats within the same treatment group. These results suggest that minocycline provides protection against neonatal systemic LPS exposure-induced enhanced pain sensitivity (allodynia and hyperalgesia), and that the protective effects may be associated with its ability to attenuate LPS-induced microglia activation, and microglia-related pro-inflammatory cytokines and pain mediators.

Disclosures: L. Tien: None. **Y. Lee:** None. **L. Fan:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.12/W11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: UC COM Seed Innovation Grant

Title: Cognitive deficits in survivors of childhood leukemia: Development of a mouse model

Authors: C. J. LAAKER[1], M. A. SMAIL[2], A. HILTZ[1], K. R. LLOYD[3], B. L. SMITH[2], J. KONSMAN[4], *T. M. REYES[3]
[2]Dept. of Psychiatry and Behavioral Neurosci., [3]Psychiatry and Behavioral Neurosci., [1]Univ. of Cincinnati, Cincinnati, OH; [4]CNRS UMR 5287 INCIA / Univ. Bordeaux, Bordeaux, France

Abstract: Survivors of childhood acute lymphoblastic leukemia (ALL) are at an increased risk for long term cognitive deficits. These deficits include decreased working memory, a 6-8 drop in IQ, and attentional impairment. Commonly used chemotherapeutic agents used in treatment of ALL are known to have widespread adverse effects on cognition. Children are especially vulnerable because the prefrontal cortex (PFC), which is largely responsible for higher cognitive function, is still developing. While human studies link childhood ALL and chemotherapy to later cognitive dysfunction, the underlying mechanisms mediating these deficits remain unknown. Thus, it is necessary to develop an animal model that can be used to investigate these mechanisms and gain a better understanding of the resulting cognitive deficits.
Male and female adolescent mice were injected with L1210 leukemic cells at P19. Three tumor cell concentrations were tested to determine a dose that balances cancer severity with survival. Starting at P21, mice received four rounds of a standard ALL chemotherapeutic regimen consisting of methotrexate, vincristine, and leucovorin every four days. Survivors were then tested in adulthood for cognitive deficits using social recognition, novel object, and operant behavioral tests. Using RT-qPCR brain tissue was analyzed for changes in genes related to

immune function and synaptic plasticity, while intestinal tissue was analyzed for markers of inflammation and expression of tight junction molecules.
Male survivors showed deficits in the novel object and social recognition tests, suggesting alterations in working memory. In males, gene expression data indicate an acute neuroinflammatory response in the PFC that normalizes by adulthood. Additionally females demonstrated long lasting changes in plasticity in the PFC. In the small intestine, male survivors had long-term elevated expression of inflammatory factors. In summary, we have created an animal model to examine the relationships between childhood cancer, chemotherapy, and long lasting cognitive deficits. Future studies will be directed at further identifying underlying mechanisms responsible for cognitive deficits and testing of potential therapeutic approaches to protect brain function during chemotherapy.

Disclosures: C.J. Laaker: None. **M.A. Smail:** None. **A. Hiltz:** None. **K.R. Lloyd:** None. **B.L. Smith:** None. **J. Konsman:** None. **T.M. Reyes:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.13/W12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 2R15NS060117-02

Title: Regulation of pro-inflammatory cytokines using brassicaceae and asteraceae plants (kale, arugula, dandelion) in diet-induced obese pre-diabetic c57bl/6 mice

Authors: *A. A. OYETUNDE, T. SIMON, D. HICKS, B. TENG, L. BANNER
California State Univ. Northridge, Northridge, CA

Abstract: Diabetes is a chronic disease that has an impact on many different organ systems in the body and can lead to serious long-term complications that are a major source of morbidity and mortality among diabetics. In addition to damage in organs such as the heart and kidney, prolonged elevation in blood sugar levels also adversely affects the central nervous system. Diet-induced obesity is an increasingly common occurrence that predisposes individuals to type-2 diabetes and contributes to complications including those of the nervous system and the immune system. Diabetes causes both structural and functional alterations often described as diabetic encephalopathy and changes in hippocampal plasticity and learning and memory have been demonstrated. Obesity increases the risk for dementia and Alzheimer's disease. These cognitive effects begin early as they are seen in children and adolescents with obesity and type 2 diabetes and include both structural and functional alterations. Obesity and type 2 diabetes leads to a

chronic state of inflammation that is thought to be important in initiating the chain of events that leads to dementia. Neuroinflammation is a complex response involving the activation of glia and the release of inflammatory mediators, such as cytokines. Cytokines involved in the inflammatory response are elevated in brains of animals fed a high fat diet (HFD) and a variety of anti-inflammatory/anti-oxidant treatments can reduce this expression and alleviate the cognitive changes. To investigate the role of dietary supplements, a high-fat diet model of prediabetes was utilized. Obese and control mice given a dietary supplement of kale, arugula, or dandelion greens for 22 weeks exhibit attenuated cognitive decline. To begin to determine the molecular mechanisms underlying this improvement, western blots were performed on hippocampal extracts. Animals on a HFD display increased levels of the astrocyte marker GFAP. Preliminary results show these elevated GFAP levels are reduced in animals on a HFD supplemented with the greens. Additional analysis will be performed with a variety of cellular markers.

Disclosures: A.A. Oyetunde: None. **T. Simon:** None. **D. Hicks:** None. **B. Teng:** None. **L. Banner:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.14/W13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Effect of myrtillocactus geometrizans (garambullo) on the stress-oxidative and memory in the hippocampus of rats fed a hypercaloric diet

Authors: *C. SANDOVAL SALAZAR[1], D. RAMÍREZ-RAYA[2], S. JIMENEZ-GARCÍA[2], X. RAMÍREZ-GOMEZ[2], V. BELTRÁN-CAMPOS[2]
[2]Salud e Ingenierías, [1]Univ. de Guanajuato, Celaya, Mexico

Abstract: The hypercaloric diets can develop overweight or obesity, as well as, oxidative stress. Some studies reported that chronic intake of a hypercaloric diet produce changes in the oxidative stress and it is accompanied by accelerate lipid peroxidation and can affect learning and memory. However, Fruits such as garambullo has a high content of phenolic compounds that show an antioxidant capability, and these could have a positive effect on the stress-oxidative produced by some diets. The aim of this study was to explore the effect phenolic compounds of garambullo (150mg of gallic acid in aqueous solution) on the lipid peroxidation and spatial memory in the hippocampus of rats fed a hypercaloric diet. A total of 40 healthy male rats were divided equally into four groups. 1) Standard diet + water; 2) Standard diet + garambullo; 3) Hypercaloric diet + water; 4) Hypercaloric diet + garambullo. All the groups were fed during six months, however in

the fifth month the second and fourth, groups received garambullo during a week. Subsequently, the water Morris maze test was performed. Lipid peroxidation levels were analyzed by measuring thiobarbituric acid reactive substances. Food intake was recordly daily. The SD-fed rat intake was approximately 50% higher than the hypercaloric groups and the garambullo have no effect to decrease lipid peroxidation and improve learning and memory. However our results demonstrated that the hypercaloric diet increases the lipid peroxidation and impairment the spatial memory. Therefore it is necessary to probe more doses of garambullo to determinate what is the optimal dose and understand how the treatment with phenolic compounds like Myrtillocactus geometrizans can improve the negative effects of hypercaloric diets, overweight or obesity.

Disclosures: C. Sandoval Salazar: None. **D. Ramírez-Raya:** None. **S. Jimenez-García:** None. **X. Ramírez-Gomez:** None. **V. Beltrán-Campos:** None.

Poster

660. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 660.15/W14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Bill and Melinda Gates Foundation Cysticercosis Elimination in Peru grants 23981 and 33848 (H.H.G.)
NIH grant 5D43TW006581 (Infectious Diseases Training Program in Peru) (R.H.G.)
NIH training grant FIC/NIH D43 TW001140, and Fondo para la Innovación, Ciencia y Tecnología FINCyT grant 129-FINCyT-IB-2013 (M.R.V.)
Innovate Perú Nro.135-PNICP-PIAP-2015

Title: Evaluation of neuronal damage in rats infected with Neurocisticercosis during a year after infection

Authors: *R. H. CÉLIZ[1], D. G. DÁVILA[2], R. H. GILMAN[3], R. P. CARMEN[2], A. D. DELGADO[2], E. BERNAL[1], M. R. VERASTEGUI[2]
[2]Infectious Dis. Lab. Research-LID, [1]Univ. Peruana Cayetano Heredia, Lima, Peru; [3]Intl. Hlth., Johns Hopkins Bloomberg Sch. of Publ. Hlth., Baltimore, MD

Abstract: Neurocysticercosis is one of the most prevalent parasitic diseases in the world. It is caused because *Taenia solium* oncospheres invade human nervous tissue and become cysticerci, causing neurocysticercosis (NCC). Due to parasite is housed in the CNS, it is difficult to study the mechanisms that are modulated in man, hence the need to use animal models that help to understand the parasite-host interaction. The presence of the larvae in the CNS generates an

inflammatory response on the part of the host, which could generate neuronal damage. Neurofilament in the form of spheroids identified in axonal inflammations was used to observe neuronal damage. This study attempted to characterize the cystic damage, by means of the presence of spheroids around a viable cyst located in parenchymal, ventricular and meningeal tissue. For that, we used a rat model for neurocysticercosis, in which 70 rats of 12 days were infected with *T. solium* oncospheres. After 1, 2, 3, 4, 6, 10 and 12 months of infection, the rats were sacrificed and sections were ordered and analyzed beginning with the visible scolex as a point of reference an area of little variability in the pathologic lesion. We found spheroids extended beyond the inflammatory reaction and gliosis into otherwise appearing normal brain tissue. In addition, there is a greater presence of spheroids in cysts located in the parenchyma compared to those located in the ventricles and meninges. Axonal damage resulting in spheroids suggest this may be an important part of the mechanisms that could explain clinical symptoms of NCC.

Disclosures: R.H. Céliz: None. **D.G. Dávila:** None. **R.H. Gilman:** None. **R.P. Carmen:** None. **A.D. Delgado:** None. **E. Bernal:** None. **M.R. Verastegui:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.01/W15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Resting state MEG signature of HIV and cannabis in young adults: Preliminary data

Authors: *S. L. NICHOLS[1], A. ROBB SWAN[2], A. ANGELES QUINTO[2], C. FENNEMA-NOTESTINE[3], R. LEE[2], M. HUANG[2]
[1]Dept. of Neurosciences, [2]Dept. of Radiology, [3]Psychiatry & Radiology, Univ. of California San Diego, La Jolla, CA

Abstract: *Background:* In the current era of antiretroviral treatment (ART), sensitive paradigms are critical for detecting the central nervous system (CNS) effects of HIV prior to structural damage or impacts on daily functioning, and for disentangling effects of HIV from comorbidities such as substance use. Magnetoencephalography (MEG) measures brain functional activation across frequency bands with fine-grained spatial and temporal resolution. This preliminary study compared brain activity of youth with HIV (YWH) and uninfected controls and examined effects of cannabis use frequency using resting state MEG. *Methods:* Eleven male youth age 18-24 with behaviorally acquired HIV (YWH) on ART and 13 age- and education-matched uninfected male controls completed cognitive tests; questionnaires to quantify cannabis use frequency; resting state MEG; and structural MRI. MEG data were processed using Fast-VESTAL source imaging program. Activation for control subjects was subtracted from that of YWH across frequency

bands and cortical areas. Activation differences were compared using t-tests with $p < 0.01$ and an additional cluster analysis with size > 500 voxels. *Results:* YWH had significantly lower verbal learning and memory. Analysis of rsMEG showed low-frequency hyperactivity for YWH in frontal pole, anterior dlPFC; alpha band hyperactivity in bilateral anterior dlPFC and right FP, anterior insula, and temporal lobe (Fig.). Beta and gamma bands showed hypoactivity for YWH in bilateral hippocampi and OFC, but hyperactivity in vmPFC. Within YWH, weekly or daily cannabis use was associated with decreased rsMEG delta-theta activity in nucleus accumbens. *Conclusions:* YWH show altered rsMEG activity relative to controls, consistent with dysfunction in episodic and working memory and emotion systems, along with decreased motivation system activity for more frequent cannabis use. Findings support further study of MEG to determine whether it can serve as a sensitive marker of early HIV CNS impact prior to functional impairment.

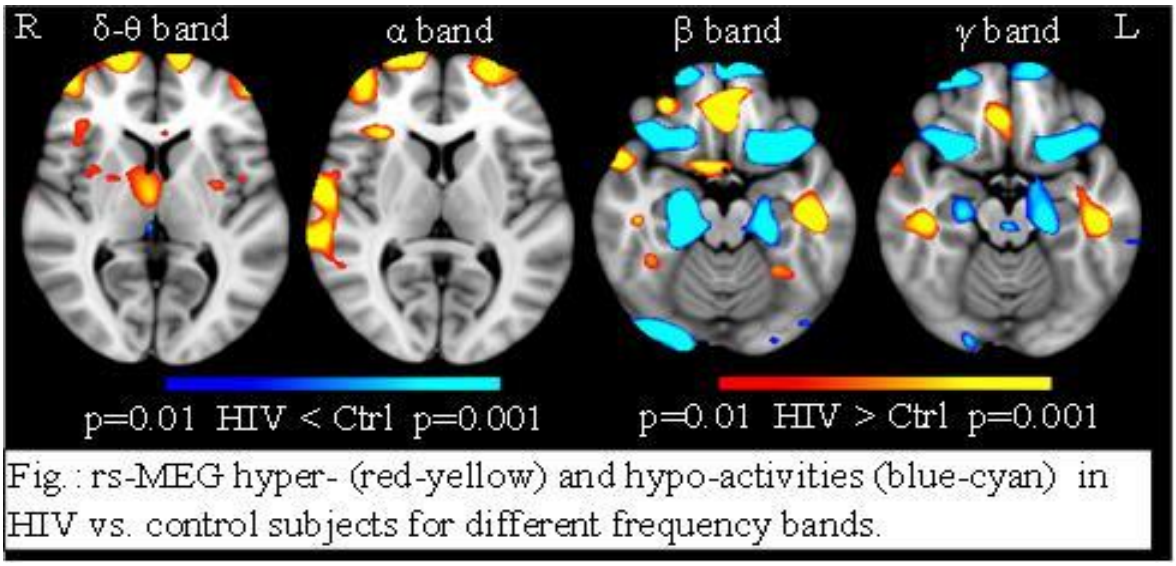


Fig. : rs-MEG hyper- (red-yellow) and hypo-activities (blue-cyan) in HIV vs. control subjects for different frequency bands.

Disclosures: S.L. Nichols: None. **A. Robb Swan:** None. **A. Angeles Quinto:** None. **C. Fennema-Notestine:** None. **R. Lee:** None. **M. Huang:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.02/W16

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant P30AI087714
NIH Grant R03MH107261
NIH Grant 1R01DE019064

NIH Grant 1R01DE022285
NIH Grant P51OD011107

Title: Neuroinflammation in pediatric HIV infection

Authors: N. ALGARZAE[1], H. CARRYL[1], M. SWANG[1], D. BREWER[1], K. VAN ROMPAY[2], K. DE PARIS[3], *M. W. BURKE[4]
[1]Physiol., Howard Univ., Washington, DC; [2]UC Davis, Davis, CA; [3]Univ. of North Carolina, Chapel Hill, NC; [4]Physiol. & Biophysics, Howard Univ. Col. of Med., Washington, DC

Abstract: As of 2013, there are 3.2 million children under the age of 15 living with HIV, globally, with an estimated one new diagnosis every 2 minutes. The devastating neurological impact of HIV on children includes loss of brain growth, motor abnormalities and cognitive dysfunction. Despite early antiretroviral treatment (ART) intervention to suppress viral load, neurological consequences of perinatal HIV-1 infection persist. Utilizing the pediatric simian immunodeficiency virus (SIV) infection model, we tested the hypothesis that early life SIV infection induces inflammation leading to neuronal loss in the hippocampus. A total of 22 infant rhesus macaques (*Macaca mulatta*) were divided into three groups: Group 1 received intravenous inoculation of SIVmac251 on postnatal day 3 (n=3) with a survival time of 6-10 weeks; Group 2 was orally challenged with SIVmac251 at week 9 of age (n=15) with a survival period of 12 weeks post-infection; and Group 3 served as uninfected controls with a survival time of 15-22 weeks. Systematic sections through the hippocampus regions CA1 to CA3 were Nissl stained and Iba1, a putative marker for microglia cells. Cell populations was determined using design-based stereology, while cell body and ramifications were quantified by the nucleator probe. We have previously reported that intravenously SIV-infected neonatal infant macaques (Group 1) displayed a 42% neuronal reduction throughout the hippocampal CA fields. The orally infected infant macaques in Group 2 displayed a 75% neuronal reduction in the CA1 compared to controls and 54% fewer neurons than Group 1 infants. The CA2 region showed a similar pattern with a 67% reduction between Group 2 and controls and a 40% difference between Group 1 and 2. Here we show elevated microglia cell size and reduced ramifications in the SIV infected subjects indicating elevated neuroinflammatory reaction. The loss of hippocampal neurons, possibly related to neuroinflammation, may contribute to the rapid neurocognitive decline associated with pediatric HIV infection. These data underscore the need for early diagnosis and treatment including therapeutics targeting the CNS.

Disclosures: N. Algarzae: None. **H. Carryl:** None. **M. Swang:** None. **D. Brewer:** None. **K. Van Rompay:** None. **K. De Paris:** None. **M.W. Burke:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.03/W17

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: South African Research Chair Initiative

Title: Change in telomere length and cognitive function over 12 months in the context of HIV, major depressive disorder and childhood trauma

Authors: *J. S. WOMERSLEY, G. SPIES, S. M. J. HEMMINGS, S. SEEDAT
Univ. of Stellenbosch, Cape Town, South Africa

Abstract: Background: HIV-associated neurocognitive disorders continue to prevail in countries affected by HIV/AIDS despite improved access to antiretroviral therapies. Previous research from our group suggested that the interaction of childhood trauma (CT) and depression may increase the risk of neurocognitive decline, and that telomere length (TL) attrition, a marker of biological aging, may mediate this relationship. We expanded our investigation of whether change in TL is predictive of declining neurocognitive function as this has implications for timely intervention. **Methods:** HIV-positive (n=61) and negative (n=49) women underwent a battery of neuropsychological tests to measure seven domains of cognitive function: motor skill, verbal fluency, attention and working memory, processing speed, learning, recall, and executive function, from which a global cognitive score was calculated. Participants completed the Childhood Trauma Questionnaire and the Centre for Epidemiological Studies Depression Scale. Quantitative polymerase chain reaction using primers specific to telomeric repeats and the reference gene human β-globin was performed on DNA extracted from peripheral blood mononuclear cells. Neurocognitive tests and TL measurements were performed at baseline and at 12 months and change scores were calculated. Multiple linear regression models using the R statistical language were used to assess the relationships between HIV, CT, depression, change in TL and change in cognitive scores. **Results:** Depressive symptoms alone, and in interaction with CT, were associated with increased TL shortening across participants ($p = 0.037$ and $p=0.017$ respectively). HIV seropositivity was strongly associated with worsening global cognitive scores over one year ($p=2 \times 10^{-4}$). Finally, the interaction of CT experience, HIV status and change in TL was associated with a decline in cognitive performance ($p=0.025$). **Conclusions:** Our longitudinal data support the deleterious impact of HIV on cognitive function and suggest that TL attrition is predictive of worse cognitive performance in the context of CT and HIV.

Disclosures: J.S. Womersley: None. **G. Spies:** None. **S.M.J. Hemmings:** None. **S. Seedat:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.04/W18

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant RO1 NS102006

Title: Divergent roles of osteopontin in the HIV-infected brain through its interaction with cell adhesion molecules & the extracellular matrix

Authors: *F. J. MAHMUD[1], A. M. BROWN[2], T. BOUCHER[1]
[1]Neurol., Johns Hopkins Hosp., Baltimore, MD; [2]Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Human immunodeficiency virus type I (HIV-1) enters the brain early, but the virus is unable to infect neurons. Instead, HIV causes direct and indirect damage by shedding viral proteins that are toxic to neurons. Neurodegeneration and memory impairment in HIV infection remain a significant clinical problem. Our aim is to identify the molecular mechanisms by which HIV directly damages neurons. The HIV-1 envelope (Env_{IIIB}) gp120 protein is known to be toxic to neurons via disruption of Ca^{2+} signaling and the induction of apoptosis.
Moreover, HIV infection of glial cells and injury to neurons leads to widespread neuroinflammation and the production of cytokines like osteopontin (OPN). OPN is a secreted phosphoglycoprotein that signals via cell adhesion molecules (CAMs)- CD44, ß1 and/or ß3 integrin receptors, which are expressed by neurons and play a role in synaptic remodeling. Based on our prior work using SHSY5Y cells and primary rat cortical neurons exposed to increasing doses of OPN, we found neuroprotective and neurite growth promoting phenotypes, suggesting that OPN can rescue Env_{IIIB} mediated neuronal injury. Hippocampal neurons (HipN) play crucial roles in memory consolidation. Therefore, in this study we used an *in vitro* model of primary rat HipN free of glia to test the hypothesis that OPN blocks neuronal injury, and to explore molecular changes in synaptic structure.
HipN were treated with Env_{IIIB} and rat OPN and subsequently stained for cytoskeletal and synaptic proteins. A significant reduction in neurofilament intensity suggested that axonal development was impaired. In addition, synaptic contacts were greatly decreased as measured by the overlap of pre- and post-synaptic proteins. We also noted an absence of dendritic spines. Activation of CREB and total CAMKII were also significantly decreased. These phenotypes were reversed by RNAi silencing of specific CAMs. These results suggest that Env_{IIIB} and OPN mediate impairment of synaptic plasticity in HipN. Interestingly, OPN can also localize to the extracellular matrix (ECM), the latter plays an important role in proper synaptic function. Recent studies show that perineuronal nets (PNN), which are specialized ECM in neurons are important

for neuronal maturation. Interestingly, we noted a degradation of PNN on neurons treated with Env_{IIIB} that could be reversed by treatment with OPN. This protection was mediated by ß1 integrins.
In conclusion, our findings indicate a differential role for OPN in HIV-mediated interactions with neurons that depend on its localization at the synapse or ECM. OPN offers protection in the ECM, but is detrimental to axons and synapses in the presence of HIV Env_{IIIB}.

Disclosures: F.J. Mahmud: None. **A.M. Brown:** None. **T. Boucher:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.05/X1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIGMS SC1GM113691
NIMH U54MD007600
NINDS R25NS094093-03

Title: A combination of free and exosomal cathepsin B released from HIV-infected macrophages trigger multiple mechanisms of neuronal dysfunction

Authors: *Y. M. CANTRES-ROSARIO[1], S. C. ORTIZ-RODRIGUEZ[1], A. SANTOS[2], L. M. MELENDEZ[1]
[1]Microbiology and Med. Zoology, Univ. of Puerto Rico, Med. Sci. Campus, San Juan, Puerto Rico; [2]Biol. Dept., Univ. of Puerto Rico, Bayamon Campus, San Juan, Puerto Rico

Abstract: Mild forms of HIV-associated neurocognitive disorders (HAND) prevail in 20-50% of the patients. HIV-infected macrophages infiltrate the brain contributing to the development of HAND. HIV-infected macrophages secrete the lysosomal protease cathepsin B (CATB) with serum amyloid p component (SAPC), as a neurotoxic protein complex. We hypothesized that CATB is released in exosomes and internalized by neurons, triggering dysfunction. We exposed neurons to histidine-tagged CATB and localized the histidine tag in neurons by flow cytometry and western blot. His-CATB was internalized by neurons (p=0.007), triggered activation of caspase 3, and decreased synaptophysin. However, pre-treating the media with anti-CATB and SAPC antibodies reduced CATB internalization by 20% and 40%, respectively, and rescued the neurons from apoptosis and synapse loss. Neurons exposed to His-CATB in HIV-infected macrophage-conditioned media (MCM) had significantly higher active caspase-3 than in uninfected media (p=0.0236). In addition, while HIV-infected MCM significantly increases amyloid beta peptides in neurons (p=0.0002), the same effect is not observed when the MCM is supplemented with His-CATB, suggesting that CATB might be degrading it. We then examined

the presence of CATB and SAPC in exosomes isolated from uninfected and HIV-infected MCM, by western blot and ELISA. Exosomes contained 34% of the total secreted CATB, as well as SAPC, CD63 and Hsp70. Exosomes from HIV-infected macrophages contained even more cathepsin B ($p=0.017$), increased the activity of caspase-3/7 in neurons (1.5 fold), and triggered neuronal death ($p=0.042$; TUNEL assay), compared to exosomes from uninfected macrophages. Pre-treating MCM with anti-CATB antibodies followed by exosome pull down, surprisingly shows that anti-CATB antibodies bind to a target in the exosome fraction. It is known that the pre-treatment of HIV-infected MCM with anti-CATB antibodies significantly decreases neuronal apoptosis, however they do not protect neurons against apoptosis triggered by exosomes derived from HIV-infected MDM. Our results suggest a novel neuronal damage process in which CATB: (1) is internalized by neurons triggering apoptosis and decreasing synapses, (2) alters the amyloid beta load, and (3) is partially secreted in exosomes inducing HIV-neurotoxicity. Since CATB and amyloid beta are elevated in the brain of HAND and Alzheimer's patients compared to normal cognition, we conclude that CATB/SAPC complex plays an important role in neurodegeneration. Further studies will allow us to determine if CATB/SAPC inhibitors could be considered as therapy candidates against HAND.

Disclosures: Y.M. Cantres-Rosario: None. **S.C. Ortiz-Rodriguez:** None. **A. Santos:** None. **L.M. Melendez:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.06/X2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIDA R21 DA041903
R00 DA033878
T32 DA007244
UNC CFAR P30 AI50410
R01 DA032933
K05 DA021696

Title: FAAH inhibition attenuates neurotoxic microglial responses via non-classic cannabinoid receptor mechanisms in a cell culture model of neuroAIDS

Authors: *D. J. HERMES[1], C. XU[1], R. B. MEEKER[2], M. NIPHAKIS[4], B. CRAVATT[4], K. MACKIE[5], A. H. LICHTMAN[6], B. M. IGNATOWSKA-JANKOWSKA[7], S. FITTING[3]
[1]Psychology & Neurosci., [2]Neurol., [3]Dept. of Psychology and Neurosci., Univ. of North Carolina, Chapel Hill, NC; [4]Dept of Mol. Med., Scripps Res. Inst., La Jolla, NC; [5]Psychol & Brain Sci., Indiana Univ. Bloomington, Bloomington, IN; [6]Pharmacol. and Toxicology, Virginia

Commonwealth Univ., Richmond, VA; [7]Neuronal Rhythms in Movement Unit, Okinawa Inst. of Sci. and Technol., Onna-son, Kunigami, Okinawa, Japan

Abstract: The HIV-1 virus is known to affect microglial immune responses which likely play a paramount role in the development of chronic neuroinflammatory conditions and neuronal damage found in HIV-1 associated neurocognitive disorders (HAND). HIV-1 Tat protein is a neurotoxin known to provoke proinflammatory responses in glial cells which precipitate neuronal injury. Drugs targeting the degradative enzymes of endogenous cannabinoids have shown promise in reducing pain and inflammation with minimal side effects in rodent models. Our lab has demonstrated that Tat can produce neurotoxic effects through microglial proinflammatory action. Considering that markers of neuroinflammation can predict the extent of neuronal injury in HAND patients, we evaluated the neurotoxic effect of Tat-exposed microglia following blockade of fatty acid amid hydrolyze (FAAH), a catabolic enzyme responsible for degradation of endocannabinoid ligands, including anandamide. We have shown before that FAAH inhibition blunts the neurotoxic effects of Tat through cannabinoid receptor mechanisms. In the present study, cultured murine microglia were incubated with Tat and/or FAAH inhibitor (PF3845). After 24 hours, microglial conditioned media was collected for neuron exposure experiments. Neuron cultures (DIV 7-11) were then exposed to diluted (1:6) microglial conditioned media, and neurotoxicity was assessed using Ca^{2+} imaging. Interestingly, PF3845's strong attenuation of microglial responses to Tat was via $CB_{1/2}$ receptor independent mechanisms. Past reports have described neuroprotective effects of non-classical cannabinoid receptors GPR55/18 on glial cells therefore to determine the role of these receptors in our cell culture model, we pretreated microglia with either antagonist, O-1918, or agonist, Abn-CBD. Preliminary data suggest that attenuation of Tat-induced increases in neuronal $[Ca^{2+}]_i$ is mediated by GPR55/18 receptors. These findings not only further elucidate the neuroprotective mechanisms of endogenous cannabinoids but also highlight the potential therapeutic benefit of the non-classic cannabinoid receptors in treating HAND and other diseases with neuroinflammatory pathologies.

Disclosures: D.J. Hermes: None. **C. Xu:** None. **R.B. Meeker:** None. **M. Niphakis:** None. **B. Cravatt:** None. **K. Mackie:** None. **A.H. Lichtman:** None. **B.M. Ignatowska-Jankowska:** None. **S. Fitting:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.07/X3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 4T32DA007097-35

NIH Grant 5R01DA007304-26

Title: HIV Tat impairs endocannabinoid signaling

Authors: *M. M. WU[1], S. A. THAYER[2]
[1]Grad. Program in Neurosci., [2]Dept. of Pharmacol., Univ. of Minnesota, Minneapolis, MN

Abstract: Despite the success of antiretroviral therapy in suppressing viral load, nearly half of the >37 million people infected with HIV experience neurocognitive impairments, collectively known as HIV-associated neurocognitive disorders (HAND). HIV-infected microglia release neurotoxic agents that induce excitotoxic synaptic injury, resulting in altered neuronal function. HIV Tat (transactivator of transcription) protein is one such neurotoxin that is thought to play a major role in the neuropathogenesis of HAND. Emerging evidence indicates a neuroprotective role of the endocannabinoid (eCB) system, which attenuates excitotoxicity. Indeed, activation of the eCB system prevents HIV-induced neurotoxicity. Whether this neuroprotective system is altered in the presence of HIV is unknown. Here, we examined modulation of the eCB system by HIV Tat in cultured hippocampal neurons. Using whole-cell patch-clamp electrophysiology, we measured adaptive changes in retrograde eCB signaling following exposure to Tat. We found that Tat exposure (50ng/mL, 24h) significantly reduced the magnitude of depolarization-induced (control: 53 ± 5%, Tat: 11 ± 6%; n=6 per group) and metabotropic suppression of excitatory postsynaptic currents (EPSCs) (control: 55 ± 4%, Tat (24h): 27 ± 3%; n=6-8 per group). These effects were not due to a loss of CB_1 receptor function, as indicated by no change in the concentration-response relationship for Win55,212-2 (a cannabinoid receptor agonist) inhibition of EPSCs in Tat-treated cultures. Thus, the mechanism of Tat-mediated reduction in eCB signaling may be postsynaptic. We hypothesize that exposure to Tat impairs synthesis of the eCB 2-arachidonoyl glycerol (2-AG). Consistent with this hypothesis, a recent study indicates that Tat sequesters phosphatidylinositol (4,5)-bisphosphate (PIP_2), a substrate required for 2-AG synthesis. The eCB system has garnered interest as a target for the treatment of neurodegenerative disorders due to its neuroprotective properties. Our data suggest that HIV Tat impairs eCB signaling. Alterations in eCB synthesis may contribute to loss of this neuroprotection, and may exacerbate the synaptodendritic injury seen in HAND. Thus, drugs that protect or enhance eCB signaling may attenuate the symptoms of HAND.

Disclosures: M.M. Wu: None. **S.A. Thayer:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.08/X4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01 MH087332, MH104131, and MH105330 (to MK)

Title: Role of microglia specific p38 signaling in neuroAIDS

Authors: *D. BHULLAR[1], R. MAUNG[1], D. OJEDA-JUÁREZ[1,2], N. YUAN[1], R. SHAH[1], M. KAUL[1,2,3]
[1]Univ. of California, Riverside, Riverside, CA; [2]Sanford Burnham Prebys Med. Discovery Inst., San Diego, CA; [3]UCSD, San Diego, CA

Abstract: Human immunodeficiency virus-1 (HIV-1) causes severe and progressive neurological impairment in humans called HIV-associated neurocognitive disorders (HAND). The HIV-1 envelope glycoprotein gp120 is an extracellular protein that is shed from infected cells and so has the potential to diffuse and interact with distant uninfected brain cells. Transgenic mice expressing HIV-1 coat glycoprotein gp120 in brain glial cells (HIVgp120tg) display neuropathological features similar to HIV dementia patients. During inflammation, p38α MAPK is known to regulate the biosynthesis of pro-inflammatory cytokines in endotoxin-stimulated monocytes. Inflammatory or stressful stimuli can also activate p38 MAPK in CNS resident cells, such as microglia, astrocytes and neurons. p38 MAPK plays crucial roles in various pathological processes associated with HIV infection, ranging from macrophage activation to neurotoxicity, impairment of neurogenesis and lymphocyte apoptosis. Thus, p38 MAPK may be an important mediator in the development of HAND and immunodeficiency during HIV-1 infection.
To determine the role of microglial p38 signaling in HIV mediated neuronal injury in vivo, we generated p38 floxed CX3CR1 Cre HIVgp120-expressing mice that have a p38 knockout specifically in microglia and macrophages. Immunofluorescence studies on brain sections of these mice were used to compare HIVgp120tg brains with and without microglia-specific p38 knockout. Non-tg brains served as controls. Brain sections were stained for neuronal MAP2 (Microtubule-associated protein 2) and astrocytic glial fibrillary acidic protein (GFAP), and nuclear DNA. Astrocytic GFAP levels remained unaffected by microglial p38 deficiency. However, we observed a significant loss of MAP2 levels compared to non-tg controls only in HIVgp120tg animals with p38-expressing microglia but not in HIVgp120-expressing brains with microglia-specific p38 knockout, indicating p38 deficiency in microglia protected neurons from HIVgp120 toxicity. Thus, our model confirmed a critical role of microglial p38 MAPK in the neurotoxicity caused by the envelope protein of HIV-1.
Supported by NIH R01 MH087332, MH104131, and MH105330 (to MK)

Disclosures: D. Bhullar: None. **R. Maung:** A. Employment/Salary (full or part-time):; University of California, Riverside. **D. Ojeda-Juárez:** A. Employment/Salary (full or part-time):; University of California. **N. Yuan:** A. Employment/Salary (full or part-time):; University of California, Riverside. **R. Shah:** A. Employment/Salary (full or part-time):; University of California. **M. Kaul:** A. Employment/Salary (full or part-time):; University of California.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.09/X5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01 DA044552-02
NIH Grant R01 NS084817-01
NIH Grant R01 DA033966-01

Title: Antiretroviral drugs increase excitability of pyramidal neurons in the medial prefrontal cortex of rats by enhancing Ca^{2+} channel function but reducing K^+ channel activity

Authors: L. CHEN[1], L. AL-HARTHI[1], *X.-T. HU[2]
[1]Microbial Pathogens and Immunity, [2]Immunology/Microbiology, Rush Univ. Med. Ctr., Chicago, IL

Abstract: Combined antiretroviral therapy (cART) suppresses HIV replication, improves immune function, and prolongs the life of HIV^+ patients. But despite cART, the prevalence of HIV-associated neurocognitive disorders (HAND) occurs in ~50% of HIV^+ patients; and that is associated with HIV-induced excitotoxicity/neurotoxicity. Recent studies reveal that many anti-retroviral medicines (ARVs) also induce neurotoxicity, including but are not limited to reduced dendritic processes, neuronal shrinkage, and mitochondrial dysfunction. Despite the well-known importance of cART in suppressing HIV, very little known is the impact of ARVs' side effects on neuronal activity in the brain regions that are susceptible and vulnerable to HIV; and whether that contribute to HAND. Lamivudine (a.k.a. 3TC) is a nucleoside reverse transcriptase inhibitor (NRTI), and one of the 3 ARVs (in combination with abacavir, ABC; and dolutegravir, DTG) that form Triumeq, a 1st-line cART regimen approved and recommended by FDA to treat HIV/AIDS. Here we assessed acute effects of 3TC and Triumeq *in vitro* on the excitability of pyramidal neurons in the medial prefrontal cortex (mPFC, a key regulator of neurocognition) using whole-cell patch-clamp recording in rat brain slices. We found that at the concentrations of 0.25-40μg/ml [1-175μM; that were comparable to those detected in the cerebral spinal fluid (CSF) of HIV^+ patients receiving Triumeq or 3TC], 3TC in bath induced a significant increase in firing of mPFC neurons (evoked by moderate stimuli that mimicked physiological excitatory inputs) in a concentration-dependent manner. This increase was associated with a significantly-enhanced Ca^{2+} influx through voltage-gated Ca^{2+} channels (by 0.25μg/ml, or 1.1μM), and a reduced activity of voltage-gated K^+ (K_v) channels and inwardly-rectifying K^+ (K_{ir}) channels. Both changes in Ca^{2+}/K^+ channel activity could depolarize the membrane potential; and therefore facilitate firing. Higher concentrations of 3TC (40μg/ml, or 175μM) began to diminish firing and Ca^{2+} channel activity in some mPFC neurons. Triumeq also significantly increased firing at a

concentration similar to that seen in CSF of HIV^+ patients (1:1, or 1x); and that was further increased by higher concentrations of the cART (10x and 100x). Collectively, these findings indicate that the NRTI 3TC increases mPFC neuronal excitability by abnormally enhancing Ca^{2+} channel activity and reducing K_v/K_{ir} channel activity; and that Triumeq also increases mPFC neuron firing, likely *via* similar mechanisms. Importantly, these novel findings suggest that chronic cART *in vivo* may exacerbate HIV-induced neuro/excitotoxicity in the mPFC.

Disclosures: L. Chen: None. **L. Al-Harthi:** None. **X. Hu:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.10/X6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Training Grant T35OD015130

Title: HIV-induced synaptic excitotoxicity via cGMP-regulated protein kinase II activation in the FIV infection model

Authors: *K. E. SZTUKOWSKI[1], K. NIP[6], P. N. OSTWALD[2], M. F. SATHLER[3], J. SHOU[3], J. H. ELDER[7], C. MILLER[4], F. HOFMANN[8], S. VANDEWOUDE[4], S. KIM[5]
[2]Cell. and Mol. Biol. Grad. Program and Mol. Biol. Grad. Program, [3]Dept. of Biomed. Sci., [4]Microbiology, Immunology, and Pathology, [5]Molecular, Cellular, and Integrative Neurosciences, [1]Colorado State Univ., Fort Collins, CO; [6]Cell. and Mol. Biol. Grad. Program, Colorado State Universtiy, Fort Collins, CO; [7]Dept. of Immunol. and Mol. Biol., The Scripps Res. Inst., La Jolla, CA; [8]Tech. Univ. of Munich, Germany, Munich, Germany

Abstract: Over half of human immunodeficiency virus (HIV)-infected individuals suffer from HIV-associated neurocognitive disorders (HAND), yet the molecular mechanisms leading to neuronal dysfunction and death are poorly understood. Feline immunodeficiency virus (FIV) naturally infects cats and shares its structure, cell tropism, and pathology with HIV, including wide-ranging neurological deficits. We employ FIV as a model to elucidate the molecular pathways underlying HIV-induced neuronal dysfunction. Among HIV-induced neuron-damaging products, the HIV envelope glycoprotein gp120 triggers elevation of intracellular Ca^{2+} in neurons, resulting in apoptosis. By quantifying neuronal activity using intracellular Ca^{2+} imaging in mouse cultured hippocampal cells, we confirmed that the FIV envelope glycoprotein gp95 also elevates intracellular Ca^{2+} activity. In addition, we revealed that gp95 interacted with the chemokine receptor, CXCR4, and facilitated the release of intracellular Ca^{2+} by the activation of the endoplasmic reticulum (ER)-associated Ca^{2+} channels, inositol triphosphate receptors (IP3Rs). This suggests that gp120 and gp95 share a core pathological process in neurons.

Significantly, gp95's stimulation of glutamate NMDA receptors activates cGMP-regulated kinase II (cGKII) through the activation of the neuronal nitric oxide synthase (nNOS)-cyclic GMP (cGMP) pathway, which increases Ca^{2+} release from the ER and promotes surface elevation of AMPA receptors, an indication of synaptic excitotoxicity. Moreover, we cultured feline hippocampal neurons and confirmed that gp95-induced Ca^{2+} excitotoxicity was mediated by CXCR4 and cGKII. These results thus provide a novel cGKII-dependent molecular understanding of synaptic dysfunction in HAND.

Disclosures: K.E. Sztukowski: None. **K. Nip:** None. **P.N. Ostwald:** None. **M.F. Sathler:** None. **J. Shou:** None. **J.H. Elder:** None. **C. Miller:** None. **F. Hofmann:** None. **S. VandeWoude:** None. **S. Kim:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.11/X7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01NS079166

Title: Wnt signaling regulates astrocyte activation during the pathogenesis of HIV-1 gp120-induced pain

Authors: *X. LIU, S. YUAN, J. ZHENG, C. BAE, S.-J. TANG
Neurosci. and Cellbiology, Univ. of Texas Med. Br. at Galveston, Galveston, TX

Abstract: HIV-related pathological pain is a debilitating complication that is associated with manifestations of neuroinflammation, including glial reaction and pro-inflammatory cytokine expression. However, the molecular mechanism regulating HIV-induced neuroinflammation remains obscure. Our studies indicate that the Wnt5a-ROR2 signaling pathway is crucial. We observed that HIV-envelope protein gp120 induced pain hypersensitivity via an MMP2-dependent IL-1β activation that is controlled by the Wnt5a in neurons and its co-receptor ROR2 in astrocytes. Although gp120 activated both microglia and astrocytes in the spinal cord, Wnt5a conditional knockout blocked the activation of astrocyte but not microglia. The Wnt5a-ROR2 signaling induced by gp120 appears to stimulate a MMP-2-dependent non-canonical pathway to control IL-1β activation. Our findings reveal a novel intercellular signaling mediated by neuronal Wnt5a and astrocytic ROR2 to regulate gp120-induced neuroinflammation and pain.

Disclosures: X. Liu: None. **S. Yuan:** None. **J. Zheng:** None. **C. Bae:** None. **S. Tang:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.12/X8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH RO1 MH087332
NIH RO1 MH104131
NIH RO1 MH105330

Title: IFNAR1 knockout affects neuronal MAP-2 expression in the presence and absence of neurotoxic HIV-1 envelope protein gp120

Authors: *H. SINGH[1], R. MAUNG[1], D. OJEDA-JUÁREZ[1,2], R. SHAH[1], M. KAUL[1,3]
[1]Biomed. Sci., Univ. of California, Riverside, Riverside, CA; [2]Sanford Burnham Prebys Med. Discovery, San Diego, AE; [3]Sanford Burnham Prebys Med. Discovery, San Diego, CA

Abstract: Infection with HIV-1 often causes brain injury, which presumably underlies HIV-associated neurocognitive disorders (HAND)/neuroAIDS. The pathogenesis of HAND is not completely understood but the most affected brain regions include frontal cortex, hippocampus, substantia nigra, putamen, basal ganglia and cerebellum. Our laboratory uses a transgenic mouse model of HIV-associated brain injury expressing the viral gp120 envelope protein in the central nervous system. These HIVgp120tg mice display key neuropathological features of human HIV brains, including loss of microtubule-associated protein (MAP)-2 positive neuronal dendrites and elevated expression of astrocytic glial fibrillary acidic protein (GFAP) compared to non-tg controls. The innate immune system responds to HIV-1 infection with the production of interferons (IFNs). Type I IFNs (IFNα and IFNβ) exert their biological functions through interaction with the type I interferon (α/β) receptors (IFNAR1 and −2). We recently showed that IFNβ prevented in vitro and in vivo neuronal injury induced by HIVgp120. Neuroprotection by IFNβ was dependent on IFNAR1. Our present study investigated the role of IFNAR1 in HIV induced brain injury by cross-breeding IFNAR1 knockout (IFNAR1KO) with HIVgp120tg mice. The brains of one-year-old IFNAR1-deficient and wild-type gp120tg mice and non-tg controls were analyzed using quantitative fluorescence microscopy. Our data shows that knocking down IFNAR1 partially ameliorates gp120-induced loss of neuronal MAP-2 in hippocampus but not cerebral cortex. Moreover, the lack of IFNAR1 itself in the absence of viral gp120 appears to diminish MAP-2 in cortex and hippocampus, suggestive of compromised neuronal dendrites. In contrast, astrocytic GFAP expression seems unaffected by the absence of IFNAR1. Altogether, our findings indicate a potentially general role for IFNAR1 in neuronal homeostasis, and a limited contribution to hippocampal injury in the presence of HIV gp120.
Supported by NIH R01 MH087332, MH104131, and MH105330 (to MK)

Disclosures: **H. Singh:** A. Employment/Salary (full or part-time):; University of California, Riverside. **R. Maung:** A. Employment/Salary (full or part-time):; University of California, Riverside. **D. Ojeda-Juárez:** A. Employment/Salary (full or part-time):; University of California, Riverside. **R. Shah:** A. Employment/Salary (full or part-time):; University of California, Riverside. **M. Kaul:** A. Employment/Salary (full or part-time):; University of California, Riverside.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.13/X9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIGMS P20GM103395
NIGMS UL1GM118991
NIGMS TL4GM118992
NIGMS RL5GM118990

Title: Co-receptor tropism in HIV-1 gp120 induced synaptic dysfunction

Authors: L. K. SMITH[1], H. K. MCKEE[2], *T. B. KUHN[3]
[1]Dept Chem. & Biochem., [2]Biol. and Wildlife, Univ. of Alaska Fairbanks, Fairbanks, AK; [3]Dept Chem. & Biochem., Univ. Alaska Fairbanks, Fairbanks, AK

Abstract: While the implementation of combination antiretroviral therapy (cART) for the treatment of HIV-1 infection has achieved a dramatic decline in deaths attributable to HIV/AIDS, it remains that upwards of 50% of individuals with long-term HIV infection are affected by the onset of progressive neurological and cognitive complications referred to under the umbrella term HIV-associated neurocognitive disorders (HAND). The viral envelope protein gp120 has been identified as a potent neurotoxin affecting neurodegeneration via mechanisms involving interactions with chemokine co-receptors CCR5 and CXCR4. Early experiments have identified a role for gp120 signaling through CCR5 and CXCR4 in the activation of a pathway common to oligomeric, soluble amyloid β linking oxidative stress to the formation of cofilin-actin bundles (rods), which have been linked to synaptic dysfunction via sequestration of cofilin and the disruption of vesicular transport resulting from occlusion of neurites containing rods. Coalescence of lipid rafts paralleled by the activation of NADPH oxidase and a requirement for the cellular prion protein (PrP^C) are central to this pathway. Here we further characterize the role of co-receptor tropism in gp120 induced lipid raft coalescence, reactive oxygen species (ROS) generation, and formation of rods in SH-SY5Y human neuroblastoma cells expressing knocked-down (siRNA) or overexpressed (lipofectamine-based plasmid transfection) levels of co-receptors CCR5 and CXCR4. Transgenic SH-SY5Y cells were exposed to $gp120_{CM}$ (R5-tropic),

$gp120_{IIIB}$ (X4-tropic), and $gp120_{MN}$ (dual-tropic) in a dose and time dependent manner. Cellular lipid raft coalescence, ROS generation, and the formation of rods were quantified for each gp120 isoform and the contribution of each receptor to gp120-mediated signaling assessed. Here, we demonstrate that $gp120_{IIIB}$ signaling through CXCR4 induces more potent raft coalescence, ROS and rod formation ($p<0.05$, one-way ANOVA w/ post-hoc Dunnett's analysis, GraphPad Prism software). These results imply a potential link between HIV co-receptor tropism and the onset of early synaptic impairment mediated by the generation of cofilin-actin rods.

Disclosures: L.K. Smith: None. **H.K. McKee:** None. **T.B. Kuhn:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.14/X10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01 MH087332
NIH R01 MH104131
NIH R01 MH105330

Title: Lipocalin-2 deficiency limits alterations of neurotransmission-related gene networks in a transgenic model of HIV-induced brain injury

Authors: *D. OJEDA-JUÁREZ[1,2], R. SHAH[1], A. B. SANCHEZ[3], R. MAUNG[1], M. KAUL[4]
[1]Univ. of California, Riverside, Riverside, CA; [2]Sanford Burnham Prebys Med. Discovery Inst., San Diego, CA; [3]UCSD, San Diego, CA; [4]Biomed. Sci., SOM, Univ. of California Riverside, Riverside, CA

Abstract: Infection with human immunodeficiency virus-1 (HIV)-1 remains a serious threat to global health. Up to 50% of HIV patients develop some form of neurological and neurocognitive complications categorized as HIV-associated neurocognitive disorders (HAND). The pathological mechanisms leading to HAND remain incompletely understood. Therefore, we studied the role of the acute phase protein lipocalin-2 (LCN2) in the context of HIV-induced brain injury. LCN2 has been shown to play a role in behaviour and cognitive function, neuronal excitability, microglial activation and as an autocrine mediator of reactive astrocytosis. In our study, we cross-bred transgenic (tg) mice expressing HIV envelope protein gp120 in their central nervous system (HIVgp120tg) with a genetic knockout of LCN2 (LCN2ko). The resulting four genotypes, wild-type, HIVgp120tg, LCN2ko, and LCN2ko x HIVgp120tg, were compared by analyzing neuropathology and changes in the expression of genes related to neurotransmission. Brains of HIVgp120tg mice display features observed in neuroHIV patients; including astrocytosis, microgliosis, and decreased synaptic connections and dendrites. Our results reveal

that expression of gp120 is associated with significant alterations in glutamatergic, GABAergic, dopaminergic and serotonergic neurotransmission systems. However, some of the changes associated with the expression of HIVgp120 are ameliorated or reversed in the absence of LCN2. Ingenuity Pathway Analysis (IPA) predicts significant alterations in biological and functional gene networks consistent with neuronal injury in HIVgp120tg and functional alterations in LCN2ko animals. However, the differential gene expression pattern in LCN2ko x gp120 animals indicates similar to normal activity or deactivation of biological pathways increased in HIVgp120tg and LCN2ko animals, suggesting that LCN2-deficiency ameliorates neuronal damage in HIVgp120tg brains. Histopathological analysis using immunofluorescence microscopy shows partial protection of neuronal dendrites in LCN2ko x gp120 animals when compared to HIVgp120tg and LCN2ko animals. Altogether, our findings suggest that LCN2 contributes to the pathological mechanisms underlying HIV-induced brain injury and thus may be a therapeutic target.

Disclosures: D. Ojeda-Juárez: None. **R. Shah:** None. **A.B. Sanchez:** None. **R. Maung:** None. **M. Kaul:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.15/X11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant MH087332
NIH Grant MH104131
NIH Grant MH105330
NIH Grant DA026306

Title: Gene expression analysis reveals sexual dimorphism for long-term effects of methamphetamine abuse and HIV-associated brain injury

Authors: *M. KAUL[1,2,3], R. MAUNG[1,2], D. OJEDA-JUAREZ[1,2], N. Y. YUAN[1,2], A. J. ROBERTS[4], A. B. SANCHEZ[2,3], _. TMARC GROUP[3]
[1]Biomed. Sci., SOM, Univ. of California Riverside, Riverside, CA; [2]Ctr. for Infectious and Inflammatory Dis., Sanford Burnham Prebys Discovery Med. Inst., La Jolla, CA; [3]Dept. of Psychiatry, Univ. of California San Diego, San Diego, CA; [4]Animal Models Core, The Scripps Res. Inst., La Jolla, CA

Abstract: Methamphetamine (METH) use is common among individuals infected with human immunodeficiency virus type-1 (HIV-1) and appears to aggravate HIV-associated neurocognitive disorders (HAND). However, the pathological mechanisms underlying the combined effects of

HIV-1 and METH on the brain remain incompletely understood. Transgenic mice expressing a soluble viral envelope protein gp120 of HIV-1 in the brain (gp120tg) develop neuropathological features similar to those observed in brains of HIV patients, including decreased synaptic and dendritic density, as well as astrocytosis and increased numbers of activated microglia. For this study we treated gp120tg mice with an escalating METH binge regimen for 25 days and analyzed the animals after 7 months at about 12 months of age. We found that prior METH treatment aggravated behavioral impairment and induced a significant reduction of neuronal dendrites and presynaptic terminals in both gp120tg and WT brains. Moreover, METH-exposed gp120tg animals displayed reduced post-tetanic potentiation, while both gp120 expression and METH treatment diminished long-term potentiation. To understand the mechanistic basis of these alterations, we analyzed the expression of components of the dopaminergic, serotonergic, GABAergic and glutaminergic neurotransmitter systems at RNA level using quantitative RT-PCR arrays. Distinct areas of the brains were analyzed separately and in combination in female and male samples. The analysis revealed that METH treatment and HIV gp120 affected all neurotransmission systems, although with significant differences between cerebral cortex, hippocampus and striatum, and between females and males. Overall, METH and viral gp120 appeared to affect expression of neurotransmission related genes the most in hippocampus, and more in cerebral cortex than striatum. Sexual dimorphism was most pronounced for the dopaminergic and serotonergic systems in all brain structures. In summary, METH treatment and viral gp120 expression compromise learning and memory function and induce neuropathology in both sexes. However, our study shows significant sexual dimorphism and differences between distinct brain regions at the RNA level in the long-term effects of METH exposure and HIV gp120 expression.

Disclosures: M. Kaul: None. **R. Maung:** None. **D. Ojeda-Juarez:** None. **N.Y. Yuan:** None. **A.J. Roberts:** None. **A.B. Sanchez:** None. **_. TMARC Group:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.16/X12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Effects of 7,8-dihydroxyflavone on glial metabolic response in the hippocampus of the HIV-1 transgenic mice

Authors: *D. PATEL
Neurol., Univ. of Maryland, Baltimore, MD

Abstract: Background: HIV-infected individuals are at a risk of developing neurological deficit. The long-term effects of HIV infection, in particular those originating in the CNS, such

as HIV associated depression, have gained attention. Animal models for HIV infection have helped to understand the pathology of the disease and developing treatment strategies. However, HIV associated depression remains poorly understood. BDNF and its receptor,TrkB, signaling represent potential therapeutic targets for major depression. The purpose of this study is to examine whether TrkB agonist 7,8-DHF shows antidepressant effects in Tg-26 mouse model. **Methods:** In this study, we examined the effects of TrkB agonist 7,8-dihydroxyflavone (7,8-DHF) (5 mg/kg) treatment for 30 days in Tg26 mice . Brains were isolated and immunohistochemical analysis was performed. **Results:** In the present study we examined the glial activity by determining GFAP and CD11b protein levels in the hippocampus of Tg26 mice before and after 7,8-DHF treatment to clarify changes in gliosis. The increased GFAP and CD11b expressions compared to control WT mice revealed the increase of glial activity and decreased after 7,8-DHF treatment, in the same condition we measured mitochondrial biogenesis and function by determining PGC-1α (mitochondrial biogenesis marker), Mfn2 (a mitochondrial fusion marker) and citrate synthase and SIRT3 (mitochondrial functional markers). Interestingly we found mitochondrial biogenesis and function are downregulated in the hippocampus of Tg26 mice compared to control group and after 7,8-DHF treatment mitochondrial biogenesis and function recovered. Furthermore, 7,8-DHF treatment also increase anti-inflammatory activities. **Conclusions:** These findings demonstrate that long lasting increased GFAP and CD11b expression in TG 26 mice indicate increased glial activity due to defect in mitochondria and 7,8-DHF treatment decreases gliosis by recovering mitochondrial homeostasis which may be involved in the impairment of the hippocampal-dependent learning of TG26 mice that plays a pivotal role in HIV associated depression and learning process.

Disclosures: D. Patel: None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.17/X13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Pharmacology T32 Training Grant

Title: Identifying a role for E2F1 in synaptodendritic damage in mouse models of HIV

Authors: *C. MEURICE[1], T. J. CIRINO[3], B.-H. KIM[5], J. P. MCLAUGHLIN[4], D. VOLSKY[6], K. L. JORDAN-SCIUTTO[2]
[2]Dept Pathology, [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Pharmacodynamics, [4]Univ. of Florida, Gainesville, FL; [5]Icahn Sch. of Med., Mt Sinai, New York City, NY; [6]Icahn Sch. of Med., Mt. Sinai, New York City, NY

Abstract: E2F1 is a transcription factor important for the transition from G1 to S phase of the cell cycle that has the potential to contribute to the development in HIV-associated neurocognitive disorders (HAND). In the CNS of HIV-infected patients with encephalitis E2F1 exhibits altered expression, and in rodent models loss of normal E2F1 function impairs synaptic health, learning and memory. To study the relationship between E2F1 and HIV-related neuropathogenesis in mice, we used two different HIV-related mouse models that exhibit neurocognitive impairment: brain-specific GFAP-driven TAT-inducible transgenic (GT-tg), in which brain-selective Tat expression is induced by activation of a doxycycline (Dox) promotor, and mouse-tropic HIV infection (EcoHIV) which utilizes a chimeric HIV that expresses ectopic murine leukemia viral envelope instead of HIV's normal envelope protein, gp120. Adult male GT-tg mice received saline or doxycycline (100mg/kg/day, i.p) for seven days to induce TAT expression or adult male wildtype mice were inoculated with EcoHIV (i.p). GT-Tg mice were euthanized 1 day after treatment and EcoHIV mice were euthanized 4-week post inoculation. Brain tissue was collected for quantification of E2F1, cleaved alpha-spectrin, pre- and post-synaptic proteins by western blot and immunofluorescence to identify potential mechanisms of synaptodendritic damage. In both models, E2F1 expression was increased which correlated with increased cleaved alpha-spectrin in GT-Tg mice and reduced PSD-95 expression in EcoHIV-infected mice. These results support our hypothesis that E2F1 plays a role in either the development or persistence of neurocognitive deficits in HIV-infected patients. Further research is required to identify a mechanistic relationship between increased E2F1 activity/expression and reduced synapse function.

Disclosures: C. Meurice: None. **T.J. Cirino:** None. **B. Kim:** None. **J.P. McLaughlin:** None. **D. Volsky:** None. **K.L. Jordan-Sciutto:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.18/X14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH DA046170

Title: Epitranscriptomics: Correlation of N^6-methyladenosine RNA methylation and pathway dysregulation in the hippocampus of HIV transgenic rats

Authors: *V. R. CANONIGO[1], F. YU[3], B. ZORMAN[4], P. SUMAZIN[4], P. P. SANNA[2]
[1]The Scripps Res. Inst., San Diego, CA; [2]Departments of Immunol. and Neurosci., The Scripps Res. Inst., La Jolla, CA; [3]European Bioinformatics Inst. (EMBL-EBI), Hinxton, United Kingdom; [4]Dept. of Pediatrics, Baylor Col. of Med., Houston, TX

Abstract: The prevalence of severe HIV-associated dementia (HAD) has decreased since the introduction of combination antiretroviral therapy (cART), milder and chronic forms of neurocognitive impairment (NCI) remain high and the pathogenic mechanisms behind them are unclear. Internal RNA modifications have been known for decades, however their roles in mRNA regulation have only recently started to be elucidated. Here to provide new insight into the molecular events leading to neurocognitive impairments (NCI) in HIV, we analyzed the most abundant mRNA modification, N6-methyladenosine (m^6A) in transcripts from the hippocampus of HIV transgenic (Tg) rats. The pattern of m^6A methylation in HIV viral transcripts largely correspond to the ones observed in cell lines and T cells. Host transcripts were found to be differentially m^6A methylated in HIV Tg rats. The functional roles of the differentially m^6A methylated pathways in HIV Tg rats is consistent with a key role of RNA methylation in the regulation of the brain transcriptome in chronic HIV disease. In particular, host transcripts show significant differential m^6A methylation of genes involved in several pathways related to neural function, suggestive of synaptodendritic injury and neurodegeneration, inflammation and immune response, as well as RNA processing and metabolism, such as splicing. Changes in m^6A methylation of neuronal and inflammation-related transcripts were usually positively correlated with differential expression, while differential m^6A methylation of pathways involved in RNA processing were more likely to be negatively correlated with transcript changes. Thus, sets of differentially m^6A methylated, ontologically-related transcripts appear to be involved in coordinated transcriptional responses in the context of neuroHIV.
The results of the study indicate that specific mRNAs are differentially affected by RNA methylation. Differentially m^6A methylated transcripts are involved in the emergence of cognitive impairment in patients with HIV. Altogether, our results support that m^6A methylation represents an additional layer of regulation of HIV and host gene expression *in vivo* that contributes significantly to the transcriptional effects of chronic HIV.

Disclosures: V.R. Canonigo: None. **F. Yu:** None. **B. Zorman:** None. **P. Sumazin:** None. **P.P. Sanna:** None.

Poster

661. Neurotoxicity, Neuroinflammation, HIV, and Infections II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 661.19/Y1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Immunomodulation of the type I interferon response protects against mortality in a murine model of neonatal HSV-1 encephalitis

Authors: *D. GIRALDO, D. R. WILCOX, R. LONGNECKER
Microbiology and Immunol., Northwestern Univ., Chicago, IL

Abstract: Newborn infection with herpes simplex virus (HSV) is a serious, life-threatening condition with an incidence of 1 in 3,200 deliveries in the U.S. Unlike adult infections, which are commonly asymptomatic, over 50% of neonatal HSV infections result in disseminated disease and encephalitis. Multiple studies suggest this stark contrast between the outcomes of newborn and adult infections is likely due to age-dependent differences in the host response to HSV infection in the CNS. However, the nature of these age-dependent differences remains largely understudied. Methods and Results: wild-type (WT) and IFN α/β receptor knock-out (IFNAR KO) 7-day-old (P7), and adult mice were intracranially inoculated with HSV-1. WT adult mice were highly resistant to infection but became susceptible in the absence of IFNAR. Newborn infections demonstrated IFNAR signaling prolongs survival in WT mice but fails to prevent mortality. Differences in susceptibility correlated with lower basal levels of IFNAR and protein kinase R (PKR) in the brain of P7 mice, which increased during the first weeks after birth to adult levels. Based on these findings, we hypothesized that increased susceptibility to HSV-1 infection of the CNS in the newborn was associated with decreased IFN signaling. Based on previous studies, we used intraperitoneal (i.p.) inoculation to model disseminated disease and hematogenous spread to the CNS, the normal route of infection in the newborn. WT and IFNAR KO P7 mice were i.p. inoculated with HSV. Functional IFNAR significantly delayed mortality suggesting it contributes to survival in response to i.p. HSV-1 infection. Because increased susceptibility to HSV-1 infection was associated with lower levels of IFNAR in the newborn brain, we hypothesized that priming the IFN response would provide protection against HSV infection. Daily doses of recombinant murine IFN-β or vehicle (PBS) were administered i.p. starting from the day before infection to newborn mice. Newborn mice were then inoculated i.p. with HSV-1 at P7. IFN-β treatment resulted in complete protection from HSV infection, and significantly higher levels of IFNAR and STAT1 compared to PBS treatment in naïve mice. We further analyzed the effect of IFN treatment on astrocyte and microglial innate responses using magnetic bead isolation. Conclusions: Our results show that increased susceptibility to HSV-1 infection in the newborn is associated with differential IFN signaling in the newborn brain. Administration of IFN-β peripherally resulted in complete protection of newborn mice from HSV-1 infection, which correlated with upregulation of IFN components in the newborn brain in response to the treatment.

Disclosures: D. Giraldo: None. **D.R. Wilcox:** None. **R. Longnecker:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.01/Y2

Topic: C.09.Stroke

Support: CIRM Grant DISC2-10714

Title: Induced human pluripotent stem cell immature astrocytes for neural repair after white matter stroke

Authors: *S. GALLEGOS[1], I. L. LLORENTE[2], W. LOWRY[2], S. CARMICHAEL[2]
[1]UCLA, Lake Balboa, CA; [2]UCLA, Los Angeles, CA

Abstract: Stroke is the leading cause of adult disability. Despite the progression of modern medicine stroke continues to afflict 800,000 individuals per year in the U.S. alone and ranks No. 5 among all causes of death. Globally, stroke is the second leading cause of death. As the population of people over the age of 45 increases, the prevalence of stroke is also expected to increase. White matter stroke accounts for approximately 30% of all stroke subtypes, yet they remain understudied due to the difficulty in reproducing these models in animals. Unlike cortical grey matter strokes, white matter strokes destroy axonal connection, astrocytes and glial cells; ultimately disrupting the connectivity of the brain. Damage to this area often results in irreversible permanent physical and mental disabilities. The brain has a very limited functional recovery in this stroke subtype. Stem/progenitor transplantation after stroke has shown promise in promoting recovery of function in other stroke subtypes. However, recent studies have failed to design a treatment model that allows for stem cells repair of brain structure or brain circuitry in white matter stroke. We have developed a model in the mouse that mimics the moderate to advance stages of white matter stroke and vascular dementia. We have designed a novel iPS-derived astrocytic therapy that is better suited to repair the damages after WMS, human iPS glial enriched progenitors (hiPSC-GEPs). hIPSC-GEPs were transplanted into the brain in the subacute period (7 days after stroke) after white matter stroke and induced endogenous oligodendrocyte differentiation and re-myelination. The hiPSC-GEPs enhanced motor recovery in comparison to other iPS-differentiated cell types. Here we test the efficacy of 5 additional hiPS-GEP lines in white matter stroke to identify the most efficacious line and to allow determination of mechanism of action, by comparing the differentiation and molecular expression profile among the 6 hiPS-GEP lines.

Disclosures: S. Gallegos: None. **I.L. Llorente:** None. **W. Lowry:** None. **S. Carmichael:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.02/Y3

Topic: C.09.Stroke

Support: National Institutes of Health Grant R01NS073815

National Institutes of Health Grant R01HL132264

Title: Paracrine signals from reactive astrocytes that control microglial proliferation after brain injury

Authors: J. J. MCINNIS[1], *J. L. SPEES[2]
[1]Univ. of Vermont, Burlington, VT; [2]Med., Univ. of Vermont, Colchester, VT

Abstract: After brain injury, reactive astrocytes and microglial cells proliferate, undergo characteristic changes in morphology, and engage in autocrine, juxtacrine, and paracrine signaling. Defining the signaling network that controls cellular function(s) within jeopardized tissue after stroke has potential to provide new treatments for stroke patients. However, specific signals released by reactive astrocytes that regulate microglia (and vice versa) remain poorly understood. Using a distal Middle Cerebral Artery Occlusion (dMCAO) model of stroke, we previously demonstrated that Endothelin receptor type B (ETB_R) signaling regulates reactive astrocyte proliferation in the peri-infarct area. To further address the role(s) of ETB_R during reactive astrogliosis, we performed microarray and ELISA assays to determine effects of altered ETB_R signaling on the paracrine activity of reactive astrocytes. Through a series of complementary approaches, here we show that ETB_R signaling controls angiopoietin-2 mRNA expression and protein secretion by reactive astrocytes that impacts microglial cell proliferation.

Disclosures: J.J. McInnis: None. **J.L. Spees:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.03/Y4

Topic: C.09.Stroke

Support: Canadian Institutes of Health Research
New World Laboratories
Medicine by Design (Canada First Research Excellence Fund)

Title: Human directly reprogrammed neural precursor cell transplants promote motor recovery in a mouse model of stroke irrespective of xenograft survival

Authors: *I. VONDERWALDE[1], A. AZIMI[2], G. ROLVINK[2], J.-E. AHLFORS[3], M. S. SHOICHET[1], C. M. MORSHEAD[2]
[1]Inst. of Biomaterials and Biomed. Engin., [2]Dept. of Surgery, Univ. of Toronto, Toronto, ON, Canada; [3]New World Labs., Laval, QC, Canada

Abstract: Stroke is one of the leading causes of acquired long-term disability worldwide. Cell transplantation is a promising therapeutic intervention; however, the identification of an optimal cell type remains a limitation to clinical translation. Here, we explored the efficacy of a novel population of clinically relevant directly reprogrammed human neural precursor cells (drNPCs) to treat the stroke-injured brain. Human drNPCs are generated from somatic cells through rapid reprogramming towards the neural lineage without the use of a viral vector or gene integration. The resulting drNPCs do not express pluripotency markers and have the ability to differentiate and give rise to cells within the neural lineage. We used a clinically relevant ET-1 model of stroke within the sensorimotor cortex of SCID/Beige mice which resulted in sustained motor deficits allowing us to determine the efficacy of drNPC transplants to promote functional recovery. We demonstrated that transplanting drNPCs 4 days after stroke leads to improved motor function within a month following transplant regardless of transplant vehicle (artificial cerebrospinal fluid or a hyaluronan methylcellulose hydrogel) and recipient sex (male or female). Importantly, when we analyzed xenograft survival, drNPCs were observed in 100% of mice at early timepoints post-transplantation (4 days) but only in ~70% of mice at 1 month following transplantation (28 days). Tissue analysis using immunostaining revealed that drNPCs that survive within the transplanted tissue primarily remain undifferentiated or give rise to astrocytes and immature neurons *in vivo*. Most interestingly, although transplanting human drNPCs was correlated with recovery, xenograft survival at 1 month was not correlated with improved functional outcomes. There was also no significant correlation between functional recovery and lesion volume or the extent of gliosis at 32 days post-stroke. These results suggest that drNPCs are a therapeutically relevant source of cells for clinical application and may be acting through a secretory mechanism to promote recovery.

Disclosures: I. Vonderwalde: None. **A. Azimi:** None. **G. Rolvink:** None. **J. Ahlfors:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); New World Laboratories, Fortuna Fix. **M.S. Shoichet:** None. **C.M. Morshead:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.04/Y5

Topic: C.09.Stroke

Support: JSPS Kakenhi 26250019 and 22122004
JSPS NEXT program (LS104)
JSPS Bilateral Open Partnership Joint Research Projects

JSPS Program for Advancing Strategic International Networks to Accelerate the Circulation of Talented Researchers (S2704)
Takeda Science Foundation
Terumo Foundation for Life Sciences and Arts
Grant-in-Aid for Research at Nagoya City University

Title: beta1 integrin signaling promotes neuronal migration along vascular scaffolds in the post-stroke brain

Authors: *T. FUJIOKA[1,2], N. KANEKO[1], I. AJIOKA[3], K. NAKAGUCHI[1], T. OMATA[1], H. OHBA[1], R. FÄSSLER[4], J. M. GARCÍA-VERDUGO[5], K. SEKIGUCHI[6], N. MATSUKAWA[2], K. SAWAMOTO[1,7]
[1]Dept. of Developmental and Regenerative Biol., [2]Dept. of Neurol. and Neurosci., Nagoya City Univ. Grad. Sch. of Med. Sci., Nagoya, Japan; [3]Ctr. for Brain Integration Res., Tokyo Med. and Dent. Univ., Tokyo, Japan; [4]Dept. of Mol. Med., Max Planck Inst. of Biochem., Martinsried, Germany; [5]Lab. of Comparative Neurobio., Univ. de Valencia, Valencia, Spain; [6]Div. of Matrixome Res. and Application, Inst. for Protein Research, Osaka Univ., Osaka, Japan; [7]Div. of Neural Develop. and Regeneration, Natl. Inst. of Physiological Sci., Okazaki, Japan

Abstract: Ischemic stroke is a main cause of chronic disability. However, there is currently no effective treatment to promote recovery from stroke-induced neurological symptoms. After stroke, newly-generated immature neurons called neuroblasts which occasionally form chain-like aggregates migrate from the neurogenic niche, ventricular-subventricular zone, toward the injured areas, where they differentiate into mature neurons. Interventions that increase the number of neuroblasts distributed at and around the lesion facilitate neurological repair in rodent models for ischemic stroke, suggesting that promoting neuroblast migration in the post-stroke brain could improve efficient neuronal regeneration. To move toward the lesion, neuroblasts form chain-like aggregates and we previously reported that they frequently migrate along blood vessels, which are thought to increase their migration efficiency. However, the molecular mechanisms regulating these migration processes are largely unknown. Here we studied the role of β1 integrin, a transmembrane receptor for extracellular matrix proteins, in these migrating neuroblasts. Using a transgenic mouse line in which β1 integrin is specifically deleted in neuroblasts after tamoxifen injection, we found that chain formation and blood vessel-guided migration of the neuroblasts were dependent on β1 integrin signaling. In vitro experiments revealed that β1 integrin was involved in adhesion of the neuroblasts to laminin coated dish surface, which is critical for their efficient somal translocation during migration. Moreover, injection of laminin-containing self-assembling gel into the post-stroke mouse brain promoted chain-formation and migration of neuroblasts toward the injured area. These data suggest that laminin signaling via β1 integrin supports vasculature-guided neuronal migration to efficiently supply neuroblasts to injured areas. This study also highlights the importance of vasculature-like scaffolds for cell migration in tissue regeneration.

Disclosures: T. Fujioka: None. **N. Kaneko:** None. **I. Ajioka:** None. **K. Nakaguchi:** None. **T. Omata:** None. **H. Ohba:** None. **R. Fässler:** None. **J.M. García-Verdugo:** None. **K. Sekiguchi:** None. **N. Matsukawa:** None. **K. Sawamoto:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.05/Y6

Topic: C.09.Stroke

Support: Accelerating Regulatory Science in Innovative Drug, Medical Device, and Regenerative Medicine (Funds from Ministry of Health, Labour and Welfare in Japan)
Research Project for Practical Applications of Regenerative Medicine (Funds from Japan Agency for Medical Research and Development)

Title: Health economical research for cell therapy against stroke

Authors: *H. SHICHINOHE[1], M. KAWABORI[2], K. HOUKIN[2]
[1]Hokkaido Univ. Hosp., Sapporo, Japan; [2]Hokkaido Univ., Sapporo, Japan

Abstract: Stroke is still a leading cause of death and disability, and despite intensive research, few treatment options exist. A recent breakthrough in cell therapy is expected to reverse the neurological sequelae of stroke. Since June 2017, we have also started the novel clinical trials, Research on advanced intervention using novel bone marrow stem cell(RAINBOW) study. It is a phase 1, open label, uncontrolled, dose response study. The primary purpose is to determine the safety of autologous BMSC product, HUNS001-01, when administered to acute ischemic stroke patients (Shichinohe H, et al. BMC Neurol. 2017;17:179). However, there are some problems to be solved before the clinical application, for examples, Ethical, Legal and Social Implications (ELSI) including Health Technology Assessment (HTA) for cell therapy. If the cost of cell therapy would be too expensive, should it be justified? National Institute for Health and Care Excellence (NICE) in UK proposed that less than £30,000 (about $40,000) per one quality-adjusted life year (QALY: Fig 1) would be appropriate. In our present study, we analyzed QALY using EQ-5D-5L and the medical cost in subjects of RAINBOW study. Because we obtained the preliminary data of QALY from 5 subjects, we will report them (Fig 2).

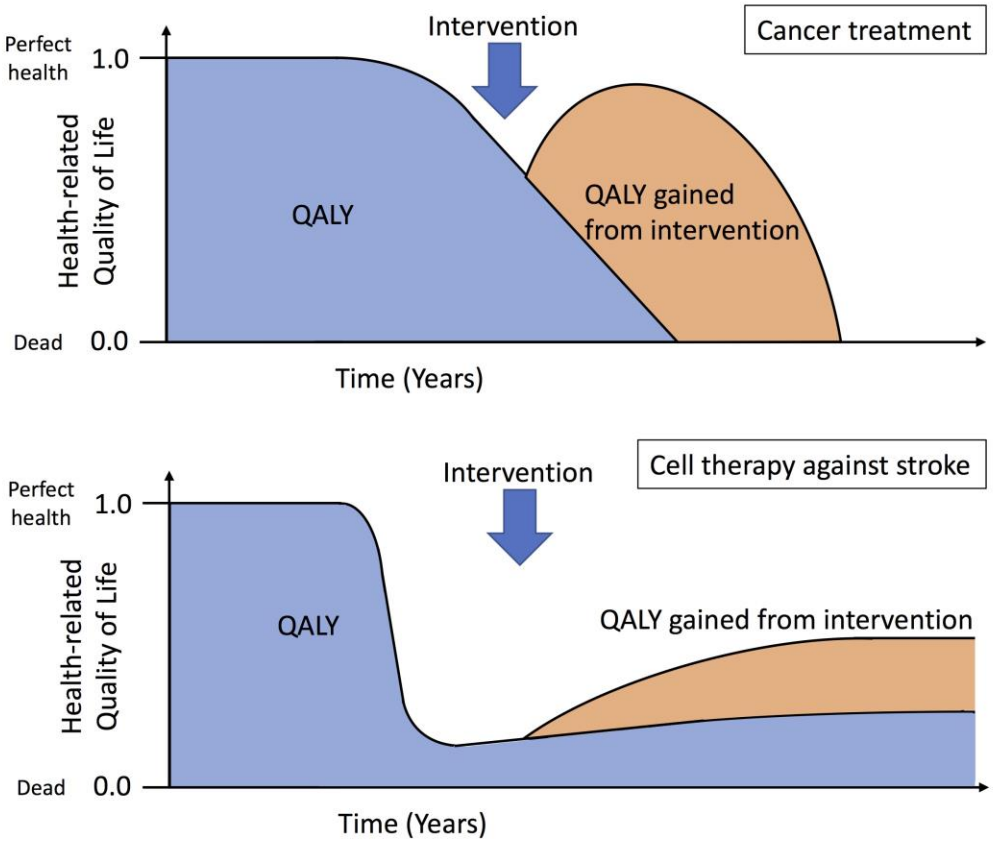

Cancer treatment
Intervention
Perfect health
1.0
Health-related Quality of Life
QALY
QALY gained from intervention
Dead
0.0
Time (Years)
Cell therapy against stroke
Intervention
Perfect health
1.0
Health-related Quality of Life
QALY
QALY gained from intervention
Dead
0.0
Time (Years)

Fig. 1

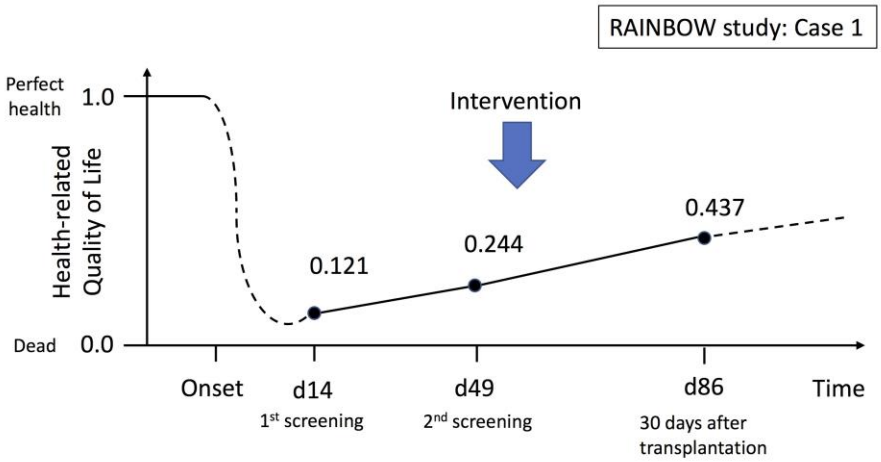

RAINBOW study: Case 1
Perfect health
1.0
Health-related Quality of Life
Intervention
0.121
0.244
0.437
Dead
0.0
Onset
d14
1st screening
d49
2nd screening
d86
30 days after transplantation
Time

Fig. 2

Disclosures: H. Shichinohe: None. **M. Kawabori:** None. **K. Houkin:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.06/Y7

Topic: C.09.Stroke

Support: NIH NINDS T32 NS082174
California Institute for Regenerative Medicine RB5-07254
Craig H. Neilsen Foundation SCIRTS-296387
NIH NCRR and NCATS UL1 TR001414
NIH R01 PQD5-CA180122
NCI Center Grant P30A062203

Title: A 3D scaffold and human cell neurovascular niche to test interactions between human neural and vascular cells *in vitro* and in stroke models

Authors: *L. A. FLANAGAN[1,2], J. ARULMOLI[2], D. T. T. PHAN[3], C. C. W. HUGHES[3]
[1]UCI Neurol., Irvine, CA; [2]Neurol. and Biomed. Engin., [3]MBB and Biomed. Engin., Univ. of California, Irvine, Irvine, CA

Abstract: Stroke is the leading cause of long term disability in the US. Current FDA-approved stroke treatments require immediate intervention, leaving 85% of patients untreated. Stem cell transplants may address this unmet need and significantly improve outcomes since cells can be transplanted days or months after stroke. Cell transplants for stroke focusing on neural or vascular brain components include neural stem/progenitor cells (NSPCs) that can generate neurons, astrocytes and oligodendrocytes or endothelial cells (ECs) that can form blood vessels. Co-transplantation of rodent NSPCs and ECs enhances the activity of both cell types, likely through synergistic communication between the cells.
We developed a human cell neurovascular niche comprised of a 3D biomaterial, human NSPCs (hNSPCs) and human ECs (hECs) to test interactions between human neural and vascular cells in vitro and in a stroke model. Our optimized 3D biomaterial scaffold of fibrin, hyaluronic acid, and laminin polymerizes effectively, ideally matches the mechanical characteristics of CNS tissue, resists rapid degradation, and supports the proliferation and differentiation of hNSPCs. Vessel formation from hECs was enhanced by hNSPCs in the scaffold, showing beneficial effects of human neural cells on human vessel formation in 3D. We found hNSPCs make a variety of factors previously identified from other cell types as positive regulators of vessel formation. We transplanted scaffolds and cells into the stroke injured rodent brain (middle cerebral artery occlusion model) and measured functional recovery and host tissue responses. HNSPCs survive

in brain tissue when transplanted with a scaffold. Rats treated with hNSPCs in a scaffold outperform control animals on rotarod tests of motor function. Host neuron survival in the penumbra region adjacent to the stroke is higher in animals treated with hNSPCs and scaffold, indicating that inclusion of an optimized scaffold improves beneficial effects of transplanted cells in stroke models. A human neurovascular niche comprised of an optimized 3D biomaterial scaffold, hNSPCs and hECs enables study of these cells' synergistic communication and can be used to assess impacts on functional recovery and host remodeling after transplant in rodent stroke models.

Disclosures: L.A. Flanagan: None. **J. Arulmoli:** None. **D.T.T. Phan:** None. **C.C.W. Hughes:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.07/Y8

Topic: C.09.Stroke

Support: Ministry of Science and ICT (18-BR-02-02)

Title: Gpr56 intronic enhancer RNA is local regulator for gene expression and potential marker for ischemic stroke

Authors: *J.-Y. JOO[1], T.-S. PARK[2], Y.-J. JANG[2], B.-G. HA[2], J.-Y. HEO[2], S.-J. JEONG[2]
[1]Neurosci., [2]Korea Brain Res. Inst., Daegu, Korea, Republic of

Abstract: In mammalian cells, transcription and gene expression are dynamically regulated by a variety of factors, and transcriptional controls are paramount for most genes. The central dogma of gene expression includes two main steps, namely, RNA transcription from the DNA sequence, followed by protein translation from the RNA sequence. Enhancer RNAs (eRNAs) are a class of long noncoding RNAs (lncRNAs) that are transcribed from DNA sequences upstream or downstream of active enhancer regions. In cortical neurons, eRNAs are synthesized in response to membrane depolarization, prior to the end of mRNA transcription. A previous study showed that eRNAs interact with negative elongation factor (NELF) to specifically regulate target gene expression, and that transcription of eRNAs is strongly correlated with mRNA transcription and protein synthesis from proximal target genes. Several genome-wide studies show that eRNAs are transcribed bidirectionally from both the plus and minus strands of DNA in mouse cortical neurons and human cancer cells, and carry unique epigenetic markers, including monomethylation at histone H3 lysine 4 (H3K4me1) and acetylation at histone H3 lysine 27 (H3K27ac). Despite these exciting findings, the mechanisms of action and roles of eRNAs in

brain-related diseases such as stroke, Alzheimer's disease, and Fragile X syndrome have not been well characterized. Here, we identified intronic activity enhancer between the first exon and the second exon at 9.9 kb away from the *Gpr56* transcription start site (TSS) through genome-wide analysis, and this intronic enhancer transcribed enhancer RNAs (eRNAs). Total RNA-seq revealed that *Gpr56* eRNA and mRNA expression levels were downregulated by hypoxia in cultured mouse neurons. The results presented here suggest that *Gpr56* gene expression is specifically regulated by the eRNA, and this process involves direct binding of the CBP transcription factor to the *Gpr56* active intronic enhancer region. Knockdown of the *Gpr56* eRNA in cortical neurons increased the protein levels of synaptophysin and PSD-95. Analyses of various brain disease model mice revealed that *Gpr56* eRNA levels were reduced only in stroke model mice. These finding suggest that *Gpr56* eRNA play as local regulator for gene expression and differential display of *Gpr56* eRNAs transcription can be potential biomarker for human brain disease, and may therefore be useful therapeutic or diagnosis targets for various diseases.

Disclosures: J. Joo: None. **T. Park:** None. **Y. Jang:** None. **B. Ha:** None. **J. Heo:** None. **S. Jeong:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.08/Y9

Topic: C.09.Stroke

Support: NIH/NINDS R01NS082225 grant

Title: The role of mir-155 in the vascular barrier function after hypoxia

Authors: *T. ROITBAK[1], T. LORDKIPANIDZE[5], E. CABALLERO-GARRIDO[2], J. PENA-PHILIPPIDES[2], A. S. GARDINER[3], R. PAN[4]
[2]Neurosurg., [3]Neurosciences, [4]Pharmaceut. Sci., [1]Univ. of New Mexico, Albuquerque, NM; [5]Ilia State Univ., Tbilisi, Georgia

Abstract: miR-155 is a multifunctional microRNA implicated in regulating various physiological and pathological processes. Our studies demonstrate that *in vivo* inhibition of miR-155 supports cerebral vasculature after the experimental stroke (mouse distal middle cerebral artery occlusion, dMCAO) by improving microvascular integrity. Electron microscopy revealed that, in contrast with the control group, miR-155 inhibitor-injected dMCAO animals demonstrated well-preserved capillary tight junctions (TJ). Based on our experimental data, the improved TJ integrity was associated with stabilization of the major TJ protein ZO-1 and correlated with activation of miR-155 target protein Rheb. miR-155 inhibition after dMCAO

significantly altered the time course and the expression levels of the major cytokines (such as IL-10 and IL-4), and considerably modified the microglia/macrophage phenotype. miR-155 downregulation was accompanied by a decreased number of phagocytically active peri-vascular microglia/macrophages. Thus, miR-155 inhibition-induced support of microvascular integrity after stroke could be also influenced by altered post-stroke inflammation. This process is mediated via the activation of miR-155 target proteins SOCS-1, SHIP-1, and C/EBP-β. Based on our *in vivo* studies, we hypothesized that miR-155 inhibition could support the barrier functions of the cultured endothelial cells. We investigated the effects of changes in miR-155 expression on the endothelial monolayer integrity and expression of TJ proteins in primary human brain microvascular endothelial cells (HBMECs) subjected to oxygen-glucose deprivation (OGD). We demonstrated that, similar to our animal studies, miR-155 silencing in the endothelial cells strengthens their barrier functions. In addition, miR-155 inhibition significantly increased the levels of major TJ proteins claudin-1 and ZO-1, while its overexpression reduced these levels. Luciferase reporter assay verified that claudin-1 is directly targeted by miR-155. Based on the immunofluorescence microscopy and Western blot analyses, we concluded that in cultured HBMECs subjected to OGD, miR-155 inhibition-induced strengthening of endothelial TJs is mediated via its target protein claudin-1.
Both our *in vivo* and *in vitro* studies support our hypothesis that cerebral regeneration after stroke can be improved by the modulation of miR-155 activity.

Disclosures: T. Roitbak: None. **T. Lordkipanidze:** None. **E. Caballero-Garrido:** None. **J. Pena-Philippides:** None. **A.S. Gardiner:** None. **R. Pan:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.09/Y10

Topic: C.09.Stroke

Support: American Heart Association grants Grant-in-aid # 16GRNT31300011 (APR)
Florida Department of Heath#7JK01 funds (HMB & APR)

Title: Monitoring post-stroke frailty in nicotine exposed female rats

Authors: *A. P. RAVAL[1], W. MORENO[4], O. FURONES-ALONSO[2], T. RUNDEK[1], W. DIETRICH, III[5], H. M. BRAMLETT[3]
[1]Neurol., [2]Neurolog. Surgery, [3]Dept Neurosurg., Univ. of Miami, Miami, FL; [4]Neurolog. Surgery, Univ. of MIami, Miami, FL; [5]Neurol Surgery, Univ. of Miami Sch. of Med., Miami, FL

Abstract: Cigarette smoking is a preventable risk factor for stroke, which is a leading cause of death and disability worldwide. Stroke disproportionately kills more women than men. Among women smokers, the risk of stroke remains high even at a young age. Smoking is a predictor of frailty, and pre-stroke smoking is associated with increased post-stroke frailty and even transient ischemic attacks that are characterized by mild ischemic episodes can result in a woman becoming frail. Frailty is characterized by an increased vulnerability to acute stressors and the reduced capacity of various bodily systems due to age-associated physiological deterioration. Although frailty is associated with increased in-hospital mortality, poorer outcome at discharge, and decreased likelihood of being discharged to the home, the prevention and treatment of smoking and stroke-associated frailty remains unaddressed. The ability to quantify frailty before and after stroke in an animal model will add to our understanding of frailty-related precursors to vascular disease. Studies performed in laboratory animals and humans support that whole body vibration (WBV) reduces or reverses pathological remodeling of bone and lessens frailty-related physiological deterioration. Adult female rats were exposed to nicotine (16 days) and to stroke by transient middle cerebral artery occlusion (tMCAO) and randomly assigned to either WBV(40 Hz; for twice a day, 5 days/week for 30 days) or control groups. We monitored the frailty index (FI) prior to and 1 month after tMCAO alone or in combination with WBV. The FI was composed of the following criteria: 1) activity levels, 2) hemodynamic measures, 3) basic metabolic status, and 4) cognitive performance of rats. Animals were sacrificed on the 30th day of WBV treatment, and brain tissue was harvested for histopathological analysis. The post-ischemic WBV intervention improves frailty parameters, reduces brain damage, and reduces frailty in control female rats, but not in the nicotine-exposed group. This suggests that WBV may be a potential therapy to reduce post-ischemic frailty and improve functional and cognitive outcomes after stroke in women. Results of this study define the frailty criterion that can be employed for future studies.

Disclosures: A.P. Raval: None. **W. Moreno:** None. **O. Furones-Alonso:** None. **T. Rundek:** None. **W. Dietrich:** None. **H.M. Bramlett:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.10/Y11

Topic: C.09.Stroke

Support: VICI 016.130.662

Title: Effect of rtms onset post-stroke: A systematic review and meta-analysis

Authors: *E. VAN LIESHOUT, V[1], B. VAN DER WORP[2], A. VISSER-MEILY[2], R. DIJKHUIZEN[2]
[1]Utrecht, Netherlands; [2]UMC Utrecht, Utrecht, Netherlands

Abstract: *Background.*Repetitive transcranial magnetic stimulation (rTMS) is a promising intervention to promote upper limb recovery in post-stroke rehabilitation. Several randomized controlled trials (RCTs) have assessed upper limb recovery after application of rTMS in different periods post-stroke, but it is unclear at which point in time rTMS is likely to be most beneficial. *Objective.*We aimed to identify the effects of different onset times of rTMS treatment on upper limb recovery after stroke. *Methods*. We searched PubMed, Embase, and the Cochrane Library to identify relevant RCTs. Meta-analyses were performed for separate and combined arm/hand motor scales, and timing of the follow-up measurement. Results.Thirty-eight studies with 1074 stroke subjects were included. Subgroup analysis of post-stroke treatment onset demonstrated benefit of rTMS applied in the early subacute phase, in comparison to the chronic phase post-stroke, on the score on the Fugl-Meyer Arm test (FMA) (<1 month; standardized mean difference (SMD), 0.77, $P < 0.001$). Tests at the level of function revealed improved upper limb outcome after rTMS (SMD 0.44, $P < 0.001$), which was not detected with tests at the level of activity (SMD 0.16, $P = 0.24$).
*Conclusions.*Based on the FMA,rTMS is more beneficial when applied in the early subacute than in the chronic phase post-stroke. Tests at the level of function are more sensitive to detect beneficial rTMS effects on upper limb outcome than tests at the level of activity. Future rTMS trials should include the FMA and work towards a core set of outcome measures.

Disclosures: B. van der Worp: None. **A. Visser-Meily:** None. **R. Dijkhuizen:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.11/Y12

Topic: C.09.Stroke

Title: Action-observation treatment through an interactive home-based platform promoting child-to-child interaction improves hand function in children suffering from unilateral cerebral palsy

Authors: *A. NUARA[1], P. AVANZINI[2], G. RIZZOLATTI[2], M. FABBRI-DESTRO[2]
[1]Neurosci. Unit, Univ. di Parma, Parma, Italy; [2]CNR Inst. of Neurosci., Parma, Italy

Abstract: By engaging the Mirror Neuron System and brain networks shared with action execution, Action Observation Therapy (AOT) proved effective in improving hand motor

function in children with unilateral cerebral palsy (UCP). The aim of this study is to assess the effectiveness of an AOT-based platform combining video stories with interactive child-to-child remote sessions (*Mirrorable*) in improving hand function in children with UCP due to perinatal stroke.
Twenty UCP children (age 5-10) with mild-to-moderate hand impairment underwent 20 sessions structured as follows: first, they had to observe and imitate a wizard performing dexterity demanding magic tricks, a child-to-child live video session aimed at practicing the same exercises. During sessions, affected limb movement was accompanied by real-time positive feedbacks thanks to a Kinect 3D camera. The paretic hand motor function was evaluated through Besta Scale: a composite scale assessing global hand motor skills (Besta G), quality of grasp (Besta A), hand involvement in specific bilateral tasks (Besta B), hand recruitment in daily activities (Besta C). Moreover, Fugl Meyer Upper Extremity, Modified Ashworth Scale, segmental strength, mood VAS and Global Impression of change (GIC), were collected. Evaluations have been performed 1 month before (Tpre), at baseline (T0) and at the end of treatment (T1).
Subjects showed a T1-T0 improvement relative to T0-Tpre in paretic hand global motor function (Besta G, 53%$\pm$41 vs 57%$\pm$41, $p<0.01$), recruitment of paretic hand in bimanual activities (Besta B, 58%$\pm$25 vs 63%$\pm$24, $p<0.01$) and a trend to significant improvement in Grasping (Besta A, 57%$\pm$31 vs 60%$\pm$36, $p=0.056$). Moreover, a significant improvement was perceived (average GIC 0.50$\pm$0.65) by families, contrarily to the pre-treatment period. Noteworthy, a correlation between motor improvement and the difference in hand motor skills relative to the peer ($r=-0.519$, $p=0.019$) was found: in other words, the better is my peer, the better is the outcome of my treatment.
Our results evidenced that AOT associated with child-to-child interaction is effective in improving hand motor functioning in UCP. Peer-to-peer difference in hand motor ability is associated to the improvement, suggesting that it is preferable for a child to observe a leading fellow with higher motor skills than his own. In conclusion, Mirrorable showed a potential helpful role in hand rehabilitation programs for children with UCP, opening traditional AOT approaches to novel social-enriched scenarios, through which children could be at the same time beneficiary and provider of motor learning processes.

Disclosures: A. Nuara: None. **P. Avanzini:** None. **G. Rizzolatti:** None. **M. Fabbri-Destro:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.12/DP05/Y13

Topic: C.09.Stroke

Support: NIH R01 NS094384
NIH R01 NS085167

Title: Vagus nerve stimulation intensity and frequency modulate cortical plasticity and motor recovery after brain injury

Authors: *D. PRUITT, T. DANAPHONGSE, M. LUTCHMAN, N. PATEL, J. LE, P. REDDY, R. RENNAKER, M. KILGARD, S. HAYS
Univ. of Texas at Dallas, Richardson, TX

Abstract: Vagus nerve stimulation (VNS) has previously been demonstrated to enhance recovery of motor function after ischemic stroke, hemorrhagic stroke, traumatic brain injury, spinal cord injury, and peripheral nerve injury. Additionally, VNS has ameliorative effects in models of post-traumatic stress disorder (PTSD) and tinnitus. VNS shows promise as a useful clinical tool to treat multiple injuries and disorders. Currently it is unknown how different intensities and frequencies of VNS affect functional recovery. In this study, we assessed three different VNS intensities (0.4 mA, 0.8 mA, and 1.6 mA) in addition to three different VNS frequencies (15 Hz, 30 Hz, 60 Hz) and determined how these parameters affected either recovery of motor function after stroke or cortical plasticity. To assess motor recovery, rats were trained on the supination task. After training to proficiency, each rat received an ischemic stroke in motor cortex. Rats then continued training for six additional weeks, during which they received VNS at one of the pre-determined intensities. We observed that rats receiving 0.8 mA VNS had enhanced motor recovery compared to all other groups of animals. Rats receiving 0.4 mA and 1.6 mA VNS did not demonstrate motor recovery compared to rats receiving no VNS at all. Following behavioral assessment, each rat received injections of a retrograde neuronal tracer in the forelimb musculature. Six days later, animals were sacrificed and brain tissue was analyzed to assess the extent of cortical cells controlling forelimb muscle that were used in the supination task. We found that animals in the 0.8 mA VNS group had significantly greater number of labeled cells than animals in all other groups. This suggests that VNS-dependent functional recovery is related to cortical plasticity in both the injured and uninjured hemispheres. Finally, to investigate the importance of frequency on cortical plasticity, we paired eating behavior with VNS for 5 days. Rats were sorted into one of the pre-determined VNS frequency groups (15 Hz, 30 Hz, or 60 Hz). After 5 days, we performed intracortical microstimulation (ICMS) motor maps of the jaw region of motor cortex to investigate if VNS resulted in expansion of jaw representation. We found that 30 Hz VNS at the 0.8 mA intensity resulted in expansion of jaw motor maps when VNS was paired with eating behavior. This data suggests that VNS paired with training at the 30 Hz frequency and 0.8 mA intensity is optimal for enhancing functional recovery after neurological injury.

Disclosures: D. Pruitt: None. **T. Danaphongse:** None. **M. Lutchman:** None. **N. Patel:** None. **J. Le:** None. **P. Reddy:** None. **R. Rennaker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vulintus, Inc. **M. Kilgard:** None. **S. Hays:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.13/Y14

Topic: C.09.Stroke

Support: California National Primate Research Center
Burroughs Wellcome Fund
UCSF Dept of Neurology

Title: Peri-lesional recordings and epidural stimulation in a non-human primate stroke model

Authors: *D. TOTTEN[1], J. M. CARMENA[2], R. J. MORECRAFT[3], K. GANGULY[1]
[1]Univ. of California, San Francisco, San Francisco, CA; [2]UC Berkeley, Berkeley, CA; [3]Univ. South Dakota Schl Med., Vermillion, SD

Abstract: Stroke is the leading cause of disability in the United States, with a substantial portion of the patients experiencing chronic motor deficits. The recovery of motor function after stroke is variable and the underlying physiological correlates of such recovery are unclear. A deeper understanding of the neural basis of motor recovery is critical to inform new avenues to improve post-stroke motor recovery. Our lab has recently conducted detailed investigations in a rodent model of stroke using rats trained to perform a reach-to-grasp task. This work establishes that low-frequency activity in peri-lesional motor cortex is correlated to the recovery of motor function after a primary motor cortex lesion. In our model, epidural stimulation delivered through skull screws boosted low-frequency activity and improved motor function. Here, we further this work by examining neural activity in the peri-lesional cortex and testing epidural stimulation as a means to boost motor recovery after stroke in non-human primates. We trained 4 male rhesus macaques between 5 and 7 years of age to perform a reach-to-grasp task and a center-out reaching task. Then, to model a stroke, aspiration was used to remove the forelimb region of primary motor cortex unilaterally. Microwire arrays or electrocorticography grids were implanted in the dorsal premotor and primary somatosensory cortex to monitor neural activity during recovery. Cranial-screws that transected the skull to contact the dura were used to deliver epidural alternating-current electrical stimulation. This exhibit includes preliminary analyses exploring the electrophysiological correlates of post-stroke recovery and the behavioral effects of epidural alternating-current electrical stimulation.

Disclosures: D. Totten: None. **J.M. Carmena:** None. **R.J. Morecraft:** None. **K. Ganguly:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.14/Y15

Topic: C.09.Stroke

Support: Development of Medical Devices and Systems for Advanced Medical Services supported by the Japan Agency for Medical Research and Development (AMED)

Title: Efficacy of multiple sessions of quadripulse stimulation in patients with stroke. A report of two cases

Authors: *K. SHINDO[1,2], F. KANEKO[2,1], M. OKAWADA[1,2], K. AKABOSHI[1,2], M. LIU[2]
[1]Dept. of Rehabil. Med., Shonan Keiiku Hosp., Fujisawa-Shi, Japan; [2]Dept. of Rehabil. Med., Keio Univ. Sch. of Med., Tokyo, Japan

Abstract: [Introduction]Quadripulse stimulation (QPS) is a new patterned repetitive transcranial magnetic stimulation (rTMS) protocol. It has been reported that the effects of QPS are less variable in healthy persons (Nakamura K, et al. 2016). Recently, rTMS has been used to improve motor function in patients with stroke (Hsu WY, et al. 2012). However, there is no evidence about the application of QPS to stroke patients. In this study, we investigated how multiple sessions of facilitative QPS over the primary motor cortex (M1) of the affected hemisphere changed motor function.[Methods]Two patients with chronic cerebral infarction gave their informed consent for participation and were included in the trial (see Table). The study was performed in accordance with the Declaration of Helsinki, was approved by the local Ethics Committee, and was registered to the UMIN Clinical Trial Registry (UMIN000032286).Because no MEPs were recorded from the affected M1, we determined the active motor threshold (AMT) of the unaffected first dorsal interosseus (FDI) muscle (MagStim 2002, The MagStim Co Ltd, UK). QPS protocol of successive four monophasic pulses delivered with an interstimulus interval (ISI) of 5 milliseconds (QPS-5) was applied to a symmetric position (mirror region) of the unaffected M1 hotspot. One therapeutic session consisted of 360 trains of four pulses (1440 pulses in total) at the intensity of 90% AMT and an intertrain interval of 5 seconds. After each QPS, the participants had kinesthetic illusion induced by visual stimulus (KiNvis) (Kaneko F, et al. 2016) 5 times a week for 2 weeks. Both conventional therapeutic exercise and Hybrid Assistive Neuromuscular Dynamic Stimulation (HANDS) therapy (Fujiwara T, et al. 2009) were also provided every day for 2 weeks.[Results]Just after one QPS session, reduced spasticity at wrist and finger flexors and improved voluntary finger movement were observed. After 10 sessions of QPS and the other interventions, both participants showed improved motor function of the paretic upper extremity (see Table). There were not definite MEPs from the affected M1.

There was no obvious adverse effect during the trial.[Conclusions]QPS may be a powerful adjunctive tool to induce motor recovery after stroke.

Demographic data and clinical evaluations			
		Patient 1	Patient 2
Age, sex		64 y/o, male	67 y/o, female
Time from onset		5 months	4 years
Edinburgh Handedness Inventory		+100	+56
Mini-Mental State Examination	Pre/Post	28/30	30/30
FMA UE motor	Pre/Post	29/38	22/31
FMA UE sensory	Pre/Post	12/12	12/12
Action Research Arm Test	Pre/Post	13/35	9/15
MAL AOU	Pre/Post	1.82/2.90	1.53/2.23
MAL QOM	Pre/Post	1.91/3.00	1.85/3.38
Box and Block Test	Pre/Post	2/16	0/1
MAS elbow flexor	Pre/Post	1+/1	1/0
MAS elbow extensor	Pre/Post	1/1	2/1
MAS wrist extensor	Pre/Post	1+/1+	3/1
MAS finger extensor	Pre/Post	1+/0	3/1
Stimulation Intensity of QPS		40%	52%
FMA, Fugl-Meyer Assessment; MAL, Motor Activity Log; AOU, amount of use scale of MAL; QOM, quality of movement scale of the MAL; MAS, Modified Ashworth Scale; QPS, quadripulse stimulation.			

Disclosures: K. Shindo: None. **F. Kaneko:** None. **M. Okawada:** None. **K. Akaboshi:** None. **M. Liu:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.15/Y16

Topic: C.09.Stroke

Support: Department of Biotechnology (DBT) India, JRF Fellowship Number DBT/2016/AIIMS/542
All India Institute of Medical Sciences New Delhi

Title: Changes in the rat brain following transient ischemic stroke - An MRI study

Authors: *T. ROY[1], R. KUMAR[2], T. G. JACOB[2], U. SHARMA[3], N. JAGANNATHAN[3]
[2]Anat., [3]Dept. of Nuclear Magnetic Resonance, [1]All India Inst. Med. Sci., New Delhi, India

Abstract: Stroke remains a leading cause of morbidity and mortality worldwide. In ischemic stroke, blockage of cerebral blood flow causes an irreversibly damaged core region and a penumbra that may get permanently damaged in the absence of an effective intervention. Using MRI we explored the changes in the rat brain following transient ischemic stroke with the passage of time. Middle cerebral artery occlusion (MCAO) surgeries were performed on adult, male, Wistar rats. The right common carotid artery was exposed and MCAO suture (Doccol corporation, USA) was introduced into the internal carotid artery through the external carotid artery to block the origin of MCA. After one-hour, the suture was retracted to allow reperfusion. MRI evaluations (n=4) were made on 7T-BIOSPEC animal MRI-scanner (Bruker, BioSpin MRI GmbH, Germany) using a 72-mm resonator as transmitter/receiver coil. T2-weighted and Diffusion-Weighted-MRI images were acquired on days 4, 14 and 28 after reperfusion. Image analysis was done using Paravision 6.0 software. Regions of interest were traced and percentage of infarction volume was calculated. Apparent diffusion coefficient (ADC) ratio was calculated for each infarct slice as ratio between the ipsilateral and contralateral ADC values. These values (infarction volume and ADC ratios) were compared between days 4, 14 and 28 using repeated measures Analysis of Variance (ANOVA). There was a significant decrease in the infarction volume with time (overall $p<0.05$). This study provides baseline data and methods that can be used to investigate the efficacy of therapeutic interventions in transient ischemia of the brain.

Disclosures: T. Roy: None. **R. Kumar:** None. **T.G. Jacob:** None. **U. Sharma:** None. **N. Jagannathan:** None.

Poster

662. Stroke Recovery: Non-Pharmacological Approaches to Therapy Cellular and Brain Stimulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 662.16/Y17

Topic: C.09.Stroke

Support: NIH Grant R01NS065172
NIH Grant R21NS095154
NIH Grant R21NS075774

NIH Grant R03NS084228
NIH Grant R21NS090609

Title: Remote ischemic post-conditioning accelerates hematoma resolution after intracerebral hemorrhage by modulating innate immune activation

Authors: *M. BRAUN[1], K. VAIBHAV[1], M. B. KHAN[2], M. HODA[3], B. BABAN[4], D. C. HESS[2], K. M. DHANDAPANI[1]
[1]Dept. of Neurosurgery, Med. Col. of Georgia, [2]Dept. of Neurology, Med. Col. of Georgia, [3]Med. Laboratory, Imaging, and Radiological Sciences, Col. of Allied Hlth. Sci., [4]Dept. of Oral Biology, Dent. Col. of Georgia, Augusta Univ., Augusta, GA

Abstract: lntracerebral hemorrhage (ICH), a devastating neurological injury that accounts for 15% of all strokes, produces the highest acute mortality and worst long-term outcomes of all stroke subtypes. Hematoma volume is an independent determinant of ICH patient outcomes, making early clot resolution a primary goal of clinical management. Herein, remote ischemic post-conditioning (RIC), the repetitive inflation-deflation of a blood pressure cuff on a limb, accelerated hematoma resolution and improved neurological outcomes after experimental ICH. Parabiosis studies revealed RIC accelerated clot resolution via a humoral-mediated mechanism. Whereas RIC increased anti-inflammatory macrophage activation, myeloid cell depletion eliminated the beneficial effects of RIC after ICH. Myeloid-specific inactivation of the metabolic regulator, 5' adenosine monophosphate-activated protein kinase (AMPK), attenuated RIC-induced anti-inflammatory macrophage polarization, delayed hematoma resolution, and worsened outcomes, providing a molecular link between RIC and macrophage activation. Finally, bone marrow chimera studies functionally implicated myeloid CD36 expression in RIC-mediated recovery, including reduced white matter injury. Thus, RIC, a clinically well-tolerated therapy, non-invasively modulates immune responses to improve ICH outcomes.

Disclosures: M. Braun: None. **K. Vaibhav:** None. **M.B. Khan:** None. **M. Hoda:** None. **B. Baban:** None. **D.C. Hess:** None. **K.M. Dhandapani:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.01/Y18

Topic: C.10. Brain Injury and Trauma

Support: New Jersey Commission on Brain Injury Research Grant CBIR16IRG017
New Jersey Commission on Brain Injury Research Grant CBIR17PIL020
Brain Health Institute Grant 2016-BHI-RUN-NJIT

National Institute of Health Grant R01 NS097750-03
USA MRMC Grant W81XWH-15-1-0303

Title: Mechanisms underlying epileptogenisis following blast induced traumatic brain injury in rat model

Authors: *M. MURUGAN[1], D. SUBRAMANIAN[2,3], V. SANTHAKUMAR[2,3], N. CHANDRA[1]
[1]Dept. of Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ; [2]Dept. of Pharmacology, Physiol. and Neurosci., Rutgers New Jersey Med. Sch., Newark, NJ; [3]Dept. of Molecular, Cell and Systems Biol., Univ. of California, Riverside, CA

Abstract: Blast-related traumatic brain injury (bTBI) is the signature injury of combat troops in military conflicts and leads to long-term physical, mental and cognitive deficits. bTBI is defined as an injury due to "primary" blast wave exposure which is distinct from impact TBI which is caused due to blunt-force injury. Although brain injury is a known precursor for the development of post traumatic epilepsy (PTE), the singular contribution of the primary blast wave to PTE remains unknown. Hence, the primary aim of this study was to investigate the effect of bTBI on epileptogenesis in a military-relevant rat model of bTBI. Ten week old male Sprague Dawley rats were subjected to mild bTBI (130 kPa) in a shock tube. The changes in cortical oscillations were examined at 4 weeks after shock wave exposure using cortical screws implanted on the skull. Interestingly, rats subject to mild bTBI developed abnormal changes in cortical oscillations with a decrease in total power of theta (4-12 Hz) and increase in power of gamma (30-90 Hz) frequency oscillations. In response to a convulsive dose of kainic acid (5mg kg^{-1} body weight, i.p), the latency to electrographic and behavioral seizures in blast-exposed animals was significantly reduced and seizure severity increased compared to sham controls. Histological and electron micrograph imaging revealed neuronal damage including diffuse axonal injury at 4h after blast exposure which may underlie the subsequent seizure susceptibility of bTBI rats. Taken together, our data suggests that a primary shock wave is sufficient to cause EEG changes reminiscent of a pre-epileptic state. Moreover, bTBI induced axonal damage may contribute to changes in the neuronal excitability and lead to epileptogenesis. This study will determine the functional outcomes following primary bTBI and further our understanding of the mechanisms underlying bTBI-induced neuropathology and help identify targets for improved therapeutic solutions.

Disclosures: M. Murugan: None. **D. Subramanian:** None. **V. Santhakumar:** None. **N. Chandra:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.02/Z1

Topic: C.10. Brain Injury and Trauma

Support: NIH T32 5T32AA7468-29

Title: Developing, validating, and phenotyping a novel mouse model of combined TBI and PTSD

Authors: *P. TEUTSCH[1], C. E. JONES[2], M. M. LIM[1,3]
[1]Veterans Affairs Portland Hlth. Care Syst., Portland, OR; [2]Behavioral Neurosci., [3]Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Traumatic brain injury (TBI) and Post traumatic stress disorder (PTSD) are highly debilitating conditions that occur in the Veteran population with dramatic prevalence. Despite their common co-occurrence and overlapping symptomology, conventional studies and treatment approaches to these diseases remain largely segregated. We hypothesize that comorbid TBI+PTSD interact to generate unique symptomology. We created a novel mouse model with which to begin exploring this condition. Using the single prolonged stress (SPS) protocol in combination with controlled cortical impact (CCI) method, four experimental groups were generated: Control, TBI, PTSD, and TBI+PTSD. Mice were tested for gait, locomotor activity, contextual fear conditioning, and acoustic prepulse inhibition. Gait and contextual fear recall were found to be significantly impaired in TBI+PTSD mice relative to controls without changes in overall locomotor activity in the home cage. Auditory sensory gating and acoustic startle were intact among the four groups. Future studies will explore pathological phenotypes, EEG/EMG recordings, and further behavioral testing in this novel combined murine model of TBI+PTSD.

Disclosures: P. Teutsch: None. **C.E. Jones:** None. **M.M. Lim:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.03/Z2

Topic: C.10. Brain Injury and Trauma

Support: CNRM-85-3389
CNRM Predoctoral Fellowship, 308049-18.01-60855

Title: Mild blast induced traumatic brain injury disrupts the neuroendocrine stress response in male and female mice

Authors: *A. L. RUSSELL[1], I. M. HERNANDEZ[2], R. J. HANDA[4], T.-Y. J. WU[3]
[1]Program in Neurosci., [2]Obstetrics and Gynecology, [3]Uniformed Services Univ., Bethesda, MD; [4]Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Traumatic brain injury (TBI) is a worldwide epidemic affecting 10 million people every year making it a leading cause of death and disability. Among military personnel, a significant portion of mild (m)TBI are induced by explosive blast devices. Mild blast TBI (mbTBI) has a unique signature, increasing susceptibility to anxiety disorders. Although the link between mbTBI and neuropsychiatric disorders is unknown, a likely candidate connecting these is the limbic-hypothalamus-pituitary-adrenal (HPA) axis. Dysregulation of the limbic-HPA axis is associated with anxiety. Therefore, we examined the effect of mbTBI (~15.5 psi) on resting and restraint-induced limbic-HPA axis reactivity in male and female mice 7-10 days post injury. mbTBI increased anxiety-like behaviors ($p<0.05$). We have previously shown that mbTBI dysregulates the HPA differently in males and females. In males, mbTBI increased ($p<0.05$) restraint-induced corticosterone (CORT) secretion, but decreased ($p<0.05$) corticotropin-releasing factor (CRF) activation, as measured by c-Fos-immunoreactivity (ir). In females, mbTBI decreased ($p<0.05$) restraint-induced CORT, but increased ($p<0.05$) CRF activation. mbTBI decreased ($p<0.05$) activation of non-neuroendocrine (pre-autonomic) CRF neurons in females, but not males, suggesting a potential link to autonomic dysregulation. mbTBI had no effect ($p>0.10$) on mineralocorticoid and glucocorticoid receptor gene expression. Surprisingly, mbTBI had no effect ($p>0.10$) on limbic expression of the well-studied CRF receptor subtype 1, a receptor involved in anxiety-like behaviors. However, mbTBI differentially altered CRFR2 gene expression. In males, mbTBI decreased ($p<0.05$) restraint-induced CRFR2 in the anterior BNST and amygdala. In females, mbTBI decreased ($p<0.05$) restraint-induced CRFR2 in the dorsal hippocampus. To further examine the impact of mbTBI on HPA axis-relevant limbic structures, we examined c-Fos-ir or EGR-1-ir, markers of neuron activation. In sham males and females, restraint increased c-Fos-ir in the infralimbic and prelimbic subdivisions of the PFC. mbTBI ablated ($p<0.05$) this restraint-induced increase. Preliminary data suggests no effect ($p>0.10$) on mbTBI on EGR-1-ir in the amygdala of males or females. Ongoing studies are examining the effect of mbTBI on c-Fos-ir in the BNST and hippocampus. Overall, our data suggests a sex-dependent dysregulation of the limbic-HPA axis stress circuitry. These data suggest that males and females utilize different strategies to cope with mbTBI, highlighting the importance of developing targeted sex dependent treatments.

Disclosures: A.L. Russell: None. **I.M. Hernandez:** None. **R.J. Handa:** None. **T.J. Wu:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.04/Z3

Topic: C.10. Brain Injury and Trauma

Support: EVER Neuro Pharma GmbH

Title: Cerebrolysin improves long-term histological outcomes and functional recovery in rats after moderate closed head injury

Authors: *Y. ZHANG[1], M. CHOPP[2,4], Y. ZHANG[2], Z. ZHANG[2], M. LU[3], T. ZHANG[3], H. WU[3], S. WINTER[5], E. DOPPLER[5], L. ZHANG[2], A. MAHMOOD[1], Y. XIONG[1]
[1]Neurosurg., [2]Neurol., [3]Biostatistics and Res. Epidemiology, Henry Ford Hosp., Detroit, MI; [4]Physics, Oakland Univ., Rochester, MI; [5]Clin. Res. and Pharmacol., EVER Neuro Pharma GmbH, Oberburgau 3, Unterach, Austria

Abstract: Background: Cerebrolysin is a neuropeptide preparation with the neurotrophic properties. The purpose of this study was to investigate the effects of Cerebrolysin on long-term functional and histological outcomes in rats after moderate closed head injury (mCHI). **Methods:** In this prospective, randomized, blinded, and placebo-controlled preclinical study, male adult Wistar rats subjected to mCHI were randomly treated with either placebo (saline, n=13) or Cerebrolysin at the optimal dose of 2.5 ml/kg (n=13) intraperitoneally administered daily for 10 days, starting at 4 h after mCHI. Animals were subjected to cognitive and sensorimotor functional tests at multiple time points, and they were sacrificed 90 days after mCHI. The brains were then processed for histological analyses of neuronal cell loss, amyloid precursor protein, axonal damage, astrogliosis, and neurogenesis. **Results:** Compared to the placebo, Cerebrolysin significantly increased the number of neuroblasts and neurogenesis in the dentate gyrus, and reduced amyloid precursor protein accumulation, astrogliosis and axonal damage in various brain regions as well as reduced neuronal cell loss in the dentate gyrus and CA3 region of the hippocampus ($p<0.05$). The global test using Generalize Estimating Equations was used to test the effect of Cerebrolysin on functional outcomes. There was a significant effect of Cerebrolysin on sensorimotor functional outcomes starting from 1 day to 3 months after injury compared to saline treatment ($p<0.05$). Cerebrolysin significantly and robustly improved long-term (up to 3 months) cognitive functional recovery measured by the Morris Water Maze, Odor Recognition, Social Interaction, and Novel Object Recognition tests. There were significant correlations between multiple histological and functional outcomes 90 days after mCHI, as detected by Pearson partial correlation analyses. **Conclusions:** Our data that Cerebrolysin significantly improves long-term histological and functional outcomes in rats after mCHI, with

functional outcomes significantly correlated with histological indices of plasticity support the efficacy of Cerebrolysin for the treatment of mCHI.

Disclosures: **Y. Zhang:** A. Employment/Salary (full or part-time):; Yanlu Zhang,Ye Xiong,Mei Lu, Talan Zhang and Hank Wu had some salary supported by EVER Neuro Pharma GmbH.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Yanlu Zhang, Ye Xiong, Dr. Michael Chopp received travel support from EVER Neuro Pharma GmbH for presenting data at scientific meetings. **M. Chopp:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); travel support for presenting data at scientific meetings. **Y. Zhang:** None. **Z. Zhang:** None. **M. Lu:** A. Employment/Salary (full or part-time):; some salary support. **T. Zhang:** A. Employment/Salary (full or part-time):; some salary support. **H. Wu:** A. Employment/Salary (full or part-time):; some salary support. **S. Winter:** A. Employment/Salary (full or part-time):; Salary. **E. Doppler:** A. Employment/Salary (full or part-time):; Salary. **L. Zhang:** None. **A. Mahmood:** None. **Y. Xiong:** A. Employment/Salary (full or part-time):; some salary. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); travel to scientific meetings.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.05/Z4

Topic: C.10. Brain Injury and Trauma

Support: NIH NS082092
NIH MH051699

Title: Lysophosphatidyl choline induces post-hemorrhagic hydrocephalus through conversion to lysophosphatidic acid via autotaxin

Authors: ***A. FRANTZ**, N. LUMMIS, P. SANCHEZ-PAVON, Y. YUNG, J. CHUN
Sanford-Burnham Med. Res. Inst., LA Jolla, CA

Abstract: Hydrocephalus, or “water on the brain”, is a common neurological disorder that occurs in 1 in 1500 live births. Hemorrhage in the developing brain commonly results in hydrocephalus, indicating that one or more blood components contribute to the disorder. The pharmacological mechanism by which this occurs, however, is not well understood. Our lab has demonstrated that lysophosphatidic acid (LPA), a lipid that doubles as a signaling molecule, is one such component and can produce post-hemorrhagic hydrocephalus (PHH) in developing mice. Specifically, we have shown that a 10 mM LPA bolus delivered to the brain ventricles of E13.5 embryonic mice causes PHH by postnatal day 10 in a receptor-dependent manner. Genetic

deletion and pharmacological blockade of LPA receptor 1 (LPA1) both attenuate the severity of PHH. Similarly, our lab has found that a 5 mM LPA bolus delivered to the brains of postnatal day 8 mice is sufficient to produce PHH after 7 days. Preliminary data indicate that an LPA bolus delivered to the brains of adult mice may contribute to post-traumatic hydrocephalus (PTH). Ependymal integrity is compromised in 33% of LPA-injected adult mice. Additionally, lysophosphatidyl choline (LPC), another abundant blood component released during hemorrhage or trauma, is an LPA precursor that we hypothesize may also lead to hydrocephalus. LPC is converted directly into LPA by the enzyme autotaxin (ATX), which is highly expressed in the choroid plexus and neural cells of the developing brain. Intraventricular delivery of LPC produces hydrocephalus similar to that of LPA. Genetic deletion of LPA1 attenuates LPC-mediated PHH, indicating that LPA receptor-mediated signaling plays a role in the progression of the disease. We hypothesize that pharmacological inhibitors of ATX and LPA1 will similarly attenuate hydrocephalus. These experiments will determine the efficacy of pharmacological intervention following hemorrhage in preventing hydrocephalus, and introduce a novel treatment for the disease.

Disclosures: A. Frantz: None. **N. Lummis:** None. **P. Sanchez-Pavon:** None. **Y. Yung:** None. **J. Chun:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.06/Z5

Topic: C.10. Brain Injury and Trauma

Title: Repeated mild closed head impacts to tau mice leads to selective neuroinflammation of the optic nerve and white matter tracts

Authors: *H. CHENG[1], J. FATHMAN[2], A. SCHUMACHER[2], J. WALKER[1]
[1]Sequencing/Expression Analysis, [2]Novartis (GNF), San Diego, CA

Abstract: Repeated mild traumatic brain injury (rmTBI) can lead to development of chronic traumatic encephalopathy (CTE). CTE is characterized by progressive neurodegeneration with presence of gliosis and hyper-phosphorylated tau. Literature reports of closed head rmTBI in rodents have yielded mixed results with regards to regions of injury and induction of phosphorylated tau. Here we report a 42 closed-head rmTBI impact paradigm on 3-4 month old male C57BL/6 mice that results in chronic inflammation of the optic nerve and associated white matter fiber tracts. We speculate these regions are most vulnerable because their anatomical location between brain and sphenoid/occipital bones facilitates biomechanical shear injury to the white matter tract during impacts. Because C57BL/6 mice do not spontaneously develop

phosphorylated tau even in the presence of rmTBI, homozygous Tau58.4 mice were subjected to injury as well. To identify the baseline pathogenesis of tauopathy and gliosis, a histological time course and peripheral immune cell profiling of these Tau58.4 mice was conducted. These mice develop minor tauopathy by 3 months of age, which begins to accelerate by 6 months of age. At 3 months post-impacts, rmTBI greatly induced inflammatory genes such as GFAP and IL-1a in the optic nerve tracts in the Tau58.4 mice, which was not nearly as robust in other brain regions. These models can reveal new information as to how rmTBI affects white matter and tau pathogenesis in the brain, and whether immune modulation can potentially alter the outcomes of the injury.

Disclosures: H. Cheng: A. Employment/Salary (full or part-time):; Novartis. **J. Fathman:** A. Employment/Salary (full or part-time):; Novartis. **A. Schumacher:** A. Employment/Salary (full or part-time):; Novartis. **J. Walker:** A. Employment/Salary (full or part-time):; Novartis.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.07/Z6

Topic: C.10. Brain Injury and Trauma

Title: The effect of repetitive mild traumatic brain injury on Alzheimer's mice containing mutations for amyloid precursor protein and tau

Authors: *N. COSCHIGANO, K. CRAVEN, S. LIPPI, J. FLINN
Psychology, George Mason, Fairfax, VA

Abstract: Traumatic brain injuries (TBI) are a known risk factor for Alzheimer’s disease (AD). Mild TBIs are the most common and often occur during adolescence. There is an increased risk of sustaining an additional TBI following the first one. This demonstrates a need to model repetitive mild TBI (rmTBI). rmTBIs lead to the development of tau tangles and amyloid plaques, similar to those in AD. Despite this, no study to date has assessed the impact of rmTBI during adolescence on a mouse model of AD containing both amyloid and tau. The proposed research aims to fill this gap in the literature by providing insight into the time-course of inflammatory markers as well as cognitive deficits in an AD mouse model following rmTBI. Offspring from the cross J20 (hAPP) and rTg4510 (TauP301L) mice (Lippi et al., 2017 SfN), were examined. This mouse demonstrates significant deficits that mimic symptoms of human AD. Furthermore, the rmTBI method utilized in our laboratory has been shown to cause spatial memory deficits 7 weeks following the last TBI and an increase in inflammatory markers in wildtype mice. We will examine the effects of rmTBI on the offspring of J20/rTg4510 mice using multiple behavioral measures, including: Morris Water Maze, Elevated Zero, Nesting,

Burrowing, and Circadian Rhythm. At eight weeks, mice will undergo rmTBI every other day for a total of 5 hits, followed by behavioral assessment at 3.5 and 8 months. This study will provide additional insight into the increased risk of the development of AD following TBI.

Disclosures: N. Coschigano: None. **K. Craven:** None. **S. Lippi:** None. **J. Flinn:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.08/Z7

Topic: C.10. Brain Injury and Trauma

Support: Hopkins Start-up fund
Brazilian Ministry of Science and Technology - CAPES

Title: Long-term effects of traumatic brain injury on fear

Authors: *J. POPOVITZ[1], K. HARKINS[1], S. P. MYSORE[2], H. M. ADWANIKAR[2]
[2]Psychological and Brain Sci., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: In humans, it is well-known that traumatic brain injury (TBI) increases the risk of psychiatric disorders, and that those effects can last for many years post-injury. Some of the most commonly experienced disorders are related to dysregulation in the fear and anxiety circuits, such as generalized anxiety disorder and post-traumatic stress disorder. In animal models, short-term effects of injury in emotional behaviors have been well-studied, and fear conditioning has been paired with TBI to emulate the fearful events that may accompany the exposure to the injury. However, it is not clear how animals exposed to a TBI react to fearful experiences in the long term. To address this issue, in this project we use a controlled cortical impact injury to examine the long-term effect of TBI on fear acquisition and extinction, and on anxiety-like behaviors. Notably, animals were tested on the open field at eight weeks post-injury, and fear conditioning was performed at nine weeks to assess long-term effects of injury. For the fear conditioning, mice were exposed to three CS-US (tone + foot shock) presentations on conditioning day, followed by three days of context and cue extinction. Behavioral results suggest impairment in fear acquisition for TBI animals, accompanied by decreased anxiety and hyperactivity in the open field test. Immunohistochemistry results indicate upregulation of GABA in the ipsilateral basolateral nucleus of the amygdala. These results will start to address long-term affective consequences of TBI and shed light on underlying neural mechanisms.

Disclosures: J. Popovitz: None. **K. Harkins:** None. **S.P. Mysore:** None. **H.M. Adwanikar:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.09/Z8

Topic: C.10. Brain Injury and Trauma

Support: This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

Title: Assessment of plasma based neuronal enriched extracellular vesicle protein cargo for potential biomarkers of mild traumatic brain injury

Authors: *N. H. GREIG[1], H. KARNATI[1], D. TWEEDIE[2], C. G. PICK[3], B. J. HOFFER[4], R. E. BECKER[5], D. KAPOGIANNIS[6]
[1]Drug Design & Develop. Section, LNS, [2]Drug Design & Develop. Section, Intramural Res. Program, Natl. Inst. on Aging, NIH, Baltimore, MD; [3]Sackler Sch. of Med., Tel-Aviv University., Tel-Aviv, Israel; [4]Aristea Translational Med., Park City, UT; [5]Neurosurg., Case Western Reserve Univ. Sch. of Med., Cleveland, OH; [6]LNS, Natl. Inst. on Aging, Baltimore, MD

Abstract: Traumatic brain injury (TBI) is a major worldwide health concern and is difficult to both diagnose and effectively treat. The overall incidence rate of TBI in the US is 577 in 100,000 (1.7 million cases per year) and the mortality rate is 17.6 in 100,000 (>51,000 deaths per year). Of these, mild (m)TBI accounts for the majority: 70%-90% of all cases. mTBI may result in loss of consciousness and/or changes in mental state that are benign but associated with neuropsychiatric symptoms. The time-dependence of the molecular mechanisms that underpin neuronal damage and recovery following a mTBI are not clearly understood, their elucidation may aid the development of effective treatments. To identify mechanisms involved in mTBI, we evaluated the protein cargo of plasma derived Extracellular Vesicles (EVs) enriched for neuronal origin. Recent studies suggest that protein profiles within bloodborne circulating EVs offer the potential to characterize initial injury and secondary pathological processes and provide potential biomarkers for clinical diagnosis. To evaluate this, 24 mice (6 weeks old) were subjected to weight drop (30 g)-induced concussive mTBI, and 10 mice to a sham procedure without injury. Blood derived plasma and cortical brain tissue samples were generated at 8, 24, 72 hr and 7, 14, 30 days post mTBI, all 4 mice per group, (sham: time 0 and 30 days, 6 and 4 mice per group). Neuronal origin enriched-EVs were extracted from plasma with a two-step process: first, total plasma EVs were isolated using Exoquick (Systems Biosciences), followed by enrichment by immuneabsorption with anti-L1CAM antibody, a transmembrane neuronal protein. EV samples were subjected to multiplexed proteomic technology (SOMAscan, SomaLogic, Inc) to profile

changes in sham vs. mTBI across time. SOMAscan technology allowed evaluation of >1000 proteins that we grouped under mechanism-based processes. Early (8 hr) changes in proteins associated with pathways related to inflammatory cytokines and acute phase responses, as well as apoptosis, cell adhesion and gluconeogenesis. These led to later (24 hr-30 days) changes in exosome markers of cytokine/chemokine activity as well as signaling cascades/proteins associated with neural development, differentiation, proliferation and migration, together with fatty acid biosynthesis and insulin resistance. Ongoing studies are cross-validating these changes by measuring key proteins in collected brain samples. Our focus is to map time-dependent proteins changes that occur in neuronal enriched, plasma derived EVs following mTBI as potential biomarkers of brain damage and response to treatment

Disclosures: H. Karnati: None. **D. Tweedie:** None. **C. G. Pick:** None. **B. J. Hoffer:** None. **R. E. Becker:** None. **D. Kapogiannis:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.10/Z9

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant 3R01NS030853-23S1

Title: Functional suppression of premotor activity in a transient model of motor cortex injury

Authors: *K. C. ELLIOTT, J. A. BORRELL, S. BARBAY, R. J. NUDO
Univ. of Kansas Med. Ctr., Kansas City, KS

Abstract: When an injury occurs to a motor region, as from a stroke or traumatic brain injury, the entire motor network is disrupted, impairing movement. We previously demonstrated in the rat that motor deficits in skilled forelimb performance, caused by a traumatic brain injury to primary motor cortex (caudal forelimb area; CFA), can be rescued when the ipsilesional premotor (i.e., the rostral forelimb area; RFA) and somatosensory forelimb (FL-S1) cortices are co-activated (Guggenmos et al., 2013). The observed motor recovery from RFA/FL-S1 co-activation began eight days after injury suggesting an acute functional reorganization of motor control, seeming to precede significant reorganization of neuroanatomical circuitry. To determine if rapid functional reorganization of sensorimotor cortices is possible without neuroanatomical changes, we are establishing a model of transient inactivation that will leave the normal cortical motor connections intact. As a first step we characterized the functional relationship between CFA and RFA. In an anesthetized rat, CFA was temporarily inactivated with muscimol. This disrupts functionality within the motor network while leaving neural

connectivity anatomically intact. Using standard intracortical microstimulation techniques (ICMS), we found that CFA inactivation completely abolished stimulation-evoked forelimb movement from RFA; neural recordings confirmed that neural suppression due to muscimol did not spread into RFA. To determine the extent to which influence of RFA output to forelimb muscles was suppressed by inactivation of CFA, intramuscular electromyographical (EMG) recordings were obtained from forelimb muscles during ICMS in RFA. EMG recordings show that muscimol caused an overall loss of muscle activation. These results show that within the intact motor network of the rat, the influence of RFA on forelimb movement is mediated through CFA. This model will be used to determine if coactivation of RFA/S1, as in Guggenmos et al. 2013, can reinstate skilled motor performance after temporary suppression of neural activity in CFA, eliminating the need for compensatory anatomical reorganization.

Disclosures: K.C. Elliott: None. **J.A. Borrell:** None. **S. Barbay:** None. **R.J. Nudo:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.11/Z10

Topic: C.10. Brain Injury and Trauma

Support: Support of Max Planck Society to JS
NIH grant RO1NS059879 toC.W.
NIH grant MH047340 to J.F.D.

Title: Action of the anti-epileptic drug phenytoin on mild traumatic brain injury in a mouse model

Authors: *J. SPIESS[1,2], C. WEISS[3], G. GARCIA[2], J. PINA-CRESPO[2], P. H. RIGBY[4], J. F. DISTERHOFT[3]
[1]Cortrop Inc., Encinitas, CA; [2]Sanford Burnham Med. Res. Inst., La Jolla, CA; [3]Dept Physiol., Northwestern Univ. Med. Sch., Chicago, IL; [4]L3 Applied Technologies, San Diego, CA

Abstract: Objective. Mild traumatic brain injury (mild TBI) is a closed-head axonal injury generated by impact from explosions, traffic accidents and sport events such as football, soccer, boxing. The axonal injury can be identified by diffusion tensor imaging (DTI). In addition to direct head trauma, peripheral pathological cellular impact-related changes may contribute to central disease. Generation of mild TBI probably induces neurodegenerative diseases such as Alzheimer's and Parkinson's disease, also depression diseases and epilepsy. In preliminary experiments, we observed the induction of absence seizures by high pressure (70 psi) exposure of a mouse model. Whether months after impact tonic-clonic seizures will appear, could not yet

be determined. To expand our experimental possibilities, we investigated the basic action of the sodium channel blocker 5,5-diphenylhydantoin (phenytoin), an antiepileptic drug, found to inhibit tonic-clonic, but not absence seizures, on mild TBI in the mouse model.
Experimental. We used male C57BL/6N mice (7-8 weeks old, single-housed) anesthetized with isoflurane. Their lungs and ears were protected with nylon ballistic coats and plastic plugs, respectively. High pressure exposure (blast) was provided by a supersonic helium wave generated in a 6 feet long and 2 inches wide aluminum tube. It hit the head of the anesthetized mouse with a reflective pressure of 69 psi for 1.4 msec. Four groups (n=10) were generated: blast/drug, blast/vehicle, no-blast/drug, no-blast/vehicle. On Day 1, 30 minutes before the blast, the mice were injected i.p. with 10 mg/kg phenytoin in vehicle (aqueous 1% Tween 80) or vehicle alone. On Day 3, the animals were trained by delay (to test non-declarative memory) or trace (to test declarative memory) fear conditioning. On Day 4, they were tested for conditioned contextual, pre-cue and cue freezing. Fecal boli were collected after each testing session. On Day 5, the mice were cardioperfused. The brains were fixed in 4% paraformaldehyde, coronally sectioned and stained for hyperphosporylated tau protein.
Results. The data were analyzed with one- or two-way anova. Fisher's PLSD tests were used for post-hoc analyses. Phenytoin enhanced differentially blast-induced contextual freezing and anxiety indicated by fecal boli increase in the absence of blast. No other specific drug effects were observed. Preliminary analysis of tau hyperphosphorylation did not show significant group or drug effects.
Conclusion. It is concluded that under blast conditions posttraumatic stress disorder (PTSD) and -based on earlier observations- absence seizures are enhanced by phenytoin, as is anxiety in the absence of blast.

Disclosures: J. Spiess: None. **C. Weiss:** None. **G. Garcia:** None. **J. Pina-Crespo:** None. **P.H. Rigby:** None. **J.F. Disterhoft:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.12/Z11

Topic: C.10. Brain Injury and Trauma

Support: NeuroSurgical Research Foundation

Title: From trauma to neurodegeneration: A one year time course of functional and neuropathological outcomes following experimental traumatic brain injury

Authors: *A. ARULSAMY[1], F. CORRIGAN[2], L. E. COLLINS-PRAINO[1]
[1]The Univ. of Adelaide, Adelaide, Australia; [2]Univ. of South Australia, Adelaide, Australia

Abstract: Although traumatic brain injury (TBI) is a risk factor for the development of dementia and motor neuron disease, the time course of this relationship and whether it depends on the severity of the original injury is not yet known. The current study investigated the functional impairments and neuropathology following either mild (mTBI), repetitive mild (rmTBI) or moderate-severe TBI (msTBI) induced by the Marmarou model of impact-acceleration. A behavioural battery was conducted at 7 days, 1, 3, 6 or 12 months post-injury (n=10-14/group/timepoint) with molecular analysis performed for markers of inflammation and neurodegenerative pathology in the cortex, hippocampus and spinal cord. Assessment of general locomotion found no significant differences relative to sham animals in any of the TBI groups at any timepoints. Anxiety-like behaviour measured on the plus maze showed that at 1 month post injury, mTBI animals spent significantly more time in the open arm ($p<0.05$), which resolved by 3 months. However, the msTBI had a significantly higher number of crossings ($p<0.01$) and open arm entries ($p<0.05$) than the shams at 1 month post injury, which gradually decreased with time, showing a significant decrease at 12 months ($p<0.05$). While depression is common in individuals following TBI, only the rmTBI group at 6 months post injury exhibited a significantly higher number of immobility episodes on the forced swim test than shams ($p<0.05$). Cognitive dysfunction is also common post TBI, and may set the stage for the later emergence of dementia. Following msTBI, animals had significantly impaired memory at 1 month ($p<0.01$), learning deficit at 6 months ($p<0.01$) and an impaired cognitive flexibility at 12 months ($p<0.01$) in relation to shams, as measured by the Barnes maze. Using a test of executive function (5-Choice Continuous Performance Task), rmTBI animals showed a significantly poorer performance at 1 month post injury while msTBI animals was significantly more liberal in response to the task at 12 months. Molecular analysis also supports the neuropathological link between TBI and neurodegeneration; hallmark neurodegenerative proteins, including pTDP-43, and oxidative stress were significantly higher in the msTBI when compared to shams at long term post injury timepoints. Taken together, the results of the current study support the emergence of cognitive dysfunction, neuropsychiatric impairments and neurodegenerative pathology chronically following TBI. The specific type of functional impairments seen post injury appear to be dependent on the nature of the original insult, with the most detrimental outcomes evident following a single moderate-severe injury.

Disclosures: F. Corrigan: None. **L.E. Collins-Praino:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.13/Z12

Topic: C.10. Brain Injury and Trauma

Support: EpiBiosS4Rx grant--5U54NS100064

Title: Longitudinal structural changes in the brain following fluid percussion injury followed by diffusion MRI

Authors: *G. SMITH[1], C. SANTANA-GOMEZ[2], R. STABA[2], N. G. HARRIS[1]
[1]Neurosurg., [2]Neurol., UCLA David Geffen Sch. of Med., Los Angeles, CA

Abstract: White matter injury is a hallmark of traumatic brain injury (TBI) and diffusion-weighted (DW) magnetic resonance imaging (MRI) is most often the clinical research tool used to investigate this. In rodent experimental models of TBI, the analysis of such data is replete with difficulties and potential biases, especially given the lack of a standard parcellated brain atlas, on-going brain atrophy, and the difficulties in co-registering the injured brain. Problems also arise when attempting to reproducibly segment white and grey matter in order to produce a white/grey matter border seed region for tract-based analysis. We attempted to solve some of these issues by developing an analysis pipeline to first quantify microstructural abnormalities by fitting the data to a tensor model to calculate scalar indices of the tensor, and by using constrained spherical deconvolution and probabilistic tractography constrained by the underlying anatomy to obtain region-to-region tract counts using a parcellated, rat brain atlas. A fixel-based analysis was also conducted to obtain counts of fiber density and fiber cross-section in order to determine the effects of the processing pipeline on injury-related differences in brain structural connectivity.
TBI was induced in adult, male, Sprague Dawley rats using the lateral fluid percussion injury model and 250 mm^3 isotropic, 3-dimensional DW MRI data (b=0,2800 s/mm^2, 42 gradient vectors) were acquired longitudinally on a 7T Bruker spectrometer at 4 post-injury time-points: 2 days, 9 days, 1 month and 5 months (n=15) and compared to sham rats (n=9) imaged at the same time-points.
Data indicate that in agreement with prior published data in this model, fixel-based analysis for fiber density does provide useful measures that discriminate between regions of injury. On-going analysis will compare the effect of pipeline processing on microstructure and tract analysis data in order to obtain the optimal method for describing injury-related differences on white matter structure.

Disclosures: G. Smith: None. **C. Santana-Gomez:** None. **R. Staba:** None. **N.G. Harris:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.14/Z13

Topic: C.10. Brain Injury and Trauma

Title: Characterization of an awake model of concussive-like injury in rats

Authors: *L. PHAM[1], H. A. KIM[1], R. C. WORTMAN[2], R. D. BRADY[2], B. R. CHRISTIE[3], G. R. DRUMMOND[1], S. R. SHULTZ[2], C. G. SOBEY[1], S. J. MCDONALD[1]
[1]Dept. of Physiology, Anat. and Microbiology, La Trobe Univ., Melbourne, Australia; [2]Dept. of Neurosci. and Med., Monash Univ., Melbourne, Australia; [3]Div. of Med. Sci., Univ. of Victoria, Victoria, ON, Canada

Abstract: Objectives: Rodent models may be able to provide important insights into some of the most pertinent issues surrounding concussion. Nonetheless, the relevance of existing models to clinical concussion is questionable, particularly regarding the use of surgery and anaesthesia, and the mechanism and severity of injury. Here, we aimed to characterize the neurobehavioural effects of an awake closed-head injury (ACHI) rat model that delivers an impact featuring clinically relevant head acceleration without use of surgery and anaesthesia.
Methods: 116, adolescent male Long-Evans rats were assigned to sham or single ACHI groups. All rats were restrained in a cone shaped bag with a 3D printed steel helmet positioned such that the impact target was centred on their left parietal cortex. Once positioned on a foam platform, a cortical impactor was used to strike the helmet target. Sham animals underwent the same procedure without impact. An array of behavioral testing was conducted post impact. Beam walk testing was used to assess sensorimotor function at baseline, 2 minutes and 24 hours post-impact. Locomotor activity was observed at 10 minutes and 24 hours using open field. Anxiety was assessed with elevated plus maze at 20 minutes and 24 hours, and finally y-maze was used to assess spatial memory at 5 minutes, 24 hours and 48 hours post-impact.
Results: Beam walk testing revealed that ACHI rats had increased hind limb slips at 2 minutes post-ACHI ($p<0.0001$), but not at 24 hours, indicating that a single injury induced transient sensorimotor deficits. Open-field showed that injured rats had transient hyperactivity, with increased distance travelled at 10 minutes ($p<0.05$) but not at 24 hours post-impact. Elevated plus maze revealed that a single ACHI increased anxiety at 20 minutes in rats, with more time spent in closed arms ($p<0.05$), less time in the centre ($p<0.05$), and trending towards less time in the open arms ($p=0.11$). A single ACHI decreased spatial memory of the Y-maze novel arm at both 5 minutes ($p<0.01$) and 24 hours ($p<0.05$) post-injury, however, by 48 hours there were no differences between sham and injured rats.
Conclusions: These findings indicate that our surgery and anaesthetic free model induces transient neurobehavioral impairments similar to that seen in clinical concussion, and as such, this model may be a valuable tool in pre-clinical concussion research.

Disclosures: L. Pham: A. Employment/Salary (full or part-time):; La Trobe University. **H.A. Kim:** A. Employment/Salary (full or part-time):; La Trobe University. **R.C. Wortman:** A. Employment/Salary (full or part-time):; Monash University. **R.D. Brady:** A. Employment/Salary (full or part-time):; Monash University. **B.R. Christie:** A. Employment/Salary (full or part-time):; University of Victoria. **G.R. Drummond:** A. Employment/Salary (full or part-time):; La Trobe University. **S.R. Shultz:** A. Employment/Salary (full or part-time):; Monash University. **C.G. Sobey:** A. Employment/Salary (full or part-time):; La Trobe University. **S.J. McDonald:** A. Employment/Salary (full or part-time):; La Trobe University.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.15/Z14

Topic: C.10. Brain Injury and Trauma

Support: EpiBiosS4Rx grant 5U54NS100064
Conacyt Scholarship 377478

Title: Evaluation of pathological high-frequency oscillations (pHFOs) during waking and sleep behavior in post-traumatic brain injury model

Authors: *C. E. SANTANA-GOMEZ[1], G. SMITH[2], N. G. HARRIS[2], R. STABA[1]
[1]Neurol., David Geffen Sch. of Med. at UCLA, Los Angeles, CA; [2]Neurosurg., Dept. Neurosurgery, UCLA, Los Angeles, CA

Abstract: Traumatic brain injury (TBI) is a serious health problem and after a severe TBI about 50% of injured individuals will develop post-traumatic epilepsy (PTE) within their lifetime. Currently there are no treatments that prevent PTE from occurring after severe TBI, and the discovery of treatments is hindered because there are no biomarkers that predict the development of PTE. Numerous studies involving patients with epilepsy and status epilepticus animal models of chronic epilepsy show pathological high frequency oscillations (pHFOs) are associated with brain areas capable of generating seizures, but only a few have studied pHFOs during the development of epilepsy. However, results from these studies suggest pHFOs could be a biomarker of epileptogenesis. Thus, the focus of our work is to develop surgical procedures and a protocol to record and analyze EEG from cortical and hippocampal sites immediately after injury in a rat model TBI, and determine whether pHFOs appear in TBI rats that develop acute (<=7 days post-injury) and/or late (>7 days post-injury) post-traumatic seizures. TBI was induced in adult, male Sprague Dawley rats (n=19) over the left hemisphere using a fluid-percussion device. During the same surgery session, electrodes were implanted within the cortex and hippocampus ipsilateral to the injury and in the cortex contralateral to the injury. A second cohort of rats ("sham"; n=6) underwent the same surgical procedures as the TBI rats, but TBI was not induced. The electrodes were mounted in 12-hole Plastic 1 pedestal and connected to the input. EEG activity was monitored 24/7 for the first week after TBI. EEG was sampled at 2 kHz/channel and bandpass settings of 0.1-500 Hz. Matlab-based RippleLab software was used to process EEG signals and detect HFOs during episodes of slow wave sleep and waking behavior. Results indicate in those rats that survive severe TBI (13 out of 19), there is a low percentage of rats (8%) that have complications from implanting electrodes immediately after TBI in the same surgical session. The initial review of the EEG recordings found acute seizures occurred in 100%

TBI rats. Review also found HFOs in all cortical and hippocampal electrodes of TBI and sham-injured rats. Ongoing analysis will assess the spatial and temporal profile of HFOs with respect to acute and late post-traumatic seizures in TBI and sham-injury rats. Epidural and/or intracerebral recording immediately after TBI could identify electrographic biomarkers of epileptogenesis that ultimately could help in the identification of patients at risk of developing PTE.

Disclosures: C.E. Santana-Gomez: None. **G. Smith:** None. **N.G. Harris:** None. **R. Staba:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.16/Z15

Topic: C.10. Brain Injury and Trauma

Support: Wellcome Trust WT092606AIA
Wellcome Trust WT091681MA
BBSRC BB/J009849/1
NIH R01-DC04290
ERC CoG, MECHIDENT

Title: MRI monitoring of macaque monkeys for neuroscience: Two case studies

Authors: *F. BALEZEAU[1], J. NACEF[1], K. L. MURPHY[2], Y. KIKUCHI[4], F. SCHNEIDER[1], F. ROCCHI[3], R. S. MUERS[5], R. FERNANDEZ-PALACIOS O'CONNOR[2], C. BLAU[2], R. C. SAUNDERS[6], M. A. HOWARD, III[7], A. THIELE[2], T. D. GRIFFITHS[5], C. I. PETKOV[2]
[1]Inst. of Neurosci., [2]Newcastle Univ., Newcastle upon Tyne, United Kingdom; [3]Inst. of Neurosci., Newcastle Univ., Newcastle, United Kingdom; [4]Newcastle Univ. Med. Sch., Newcastle upon Tyne, United Kingdom; [5]Inst. of Neurosci., Newcastle upon Tyne, United Kingdom; [6]Lab. Neuropsychol, NIMH, Bethesda, MD; [7]Univ. of Iowa Hosp. and Clinics, Iowa City, IA

Abstract: Information from Magnetic Resonance Imaging (MRI) can be useful for managing infrequent neurological or neuroscientific cases, provided that there are no MRI contra-indications precluding scanning. Here we report on the utility of MRI-based monitoring in two cases with rhesus macaques. In both cases the monkeys presented with subtle to mild clinical signs, were well otherwise and without a significant increase in welfare impact, hence they were identified as suitable candidates for clinical investigation, MRI-based monitoring and treatment. The first case (M1) presented with left-handed weakness contralateral to a recording chamber

over sensory motor cortex above the central sulcus. T1 and T2 weighted MRI imaging (4.7 Tesla, Bruker) identified two suspected sub-dural abscess sites. These were targeted for antibiotic treatment and either aspiration or implant modification. Thereafter the animal's hand use returned to normal. The second case (M2) presented with left-handed weakness from a different basis. T1, T2 and proton density scans identified a suspected internal cerebral haemorrhage in the acute/subacute stage (hypo-intense signal on both T1 and T2), presenting as an area of MRI signal loss. Continued MRI monitoring coincided with a return to unremarkable behaviour and a substantial reduction in the size of the affected area combined with signal resolution under which normal tissue could once again be observed. Time of flight MRI angiography identified a subdural venous drainage network and recordings were planned to avoid it. In summary, MRI assists in a precise diagnosis of cerebral events and can be a valuable addition to clinical treatment to ensure resolution.

Disclosures: F. Balezeau: None. **J. Nacef:** None. **K.L. Murphy:** None. **Y. Kikuchi:** None. **F. Schneider:** None. **F. Rocchi:** None. **R.S. Muers:** None. **R. Fernandez-Palacios O'Connor:** None. **C. Blau:** None. **R.C. Saunders:** None. **M.A. Howard:** None. **A. Thiele:** None. **T.D. Griffiths:** None. **C.I. Petkov:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.17/Z16

Topic: C.10. Brain Injury and Trauma

Support: Project no. LQ1605 from the National Program of Sustainability II (MEYS CR)
Technology Agency of the CR (TA CR), project no. TG02010048

Title: Role of amyloid precursor protein in axonal pathology

Authors: *V. LACOVICH[1], K. TEXLOVÁ[1], B. P. HEAD[2], V. POZO DEVOTO[1], M. NOVAKOVÁ[1], M. FEOLE[1], G. STOKIN[1]
[1]TAP, Intl. Clin. Res. Ctr. FNUSA-ICRC, Brno, Czech Republic; [2]Anesthesiol., VA Med. Ctr., San Diego, CA

Abstract: Several studies demonstrated an association between Traumatic Brain Injury (TBI), memory impairments and the risk of developing neurodegenerative disorders including Chronic Traumatic Encephalopathy (CTE) and Alzheimer's Disease (AD). Post-mortem TBI brains exhibit extensive axonal pathology, often in the form of diffuse axonal injury (DAI), which can be best identified by aberrant axonal accumulation of the Amyloid Precursor Protein (APP), best known for its intimate link to the pathogenesis of AD. Despite likely non-coincidental

association between TBI, CTE and AD clinically and biochemically, the mechanisms leading to aberrant accumulation of APP in response to axonal injury remain largely unknown. To elucidate the role of APP in in response to axonal injury we decided to study first the response of the axons to TBI in wildtype (WT) and APP deficient (APP KO) mice in the C57Bl/6 genetic background. More specifically, in order to produce TBI we adopted the cortical controlled impact protocol, which is a well-established mouse model of TBI. In short, reaching adulthood 1/3 of littermates underwent TBI (TBI), 1/3 of littermates underwent sham surgery of the skull (Sham), while the remaining 1/3 did not undergo any manipulation (Control). Following manipulations mice were weighted and tested on inverted grid weekly for a total of 8 weeks. This was followed by an open field test and last by the 24h fear conditioning paradigm. Mice were then sacrificed and perfused and the brains collected for immunochemical and biochemical studies. Consistent with previous studies, APP KO mice exhibited reduced body weight compared to WT littermates. On inverted grid WT control mice performed best compared to all other mice with APP KO mice demonstrating the most severe phenotype. Intriguingly, behavioral assessment of WT and APP KO mice following TBI reveals APP KO specific as well as TBI specific phenotypes. Immunohistochemically, all mice demonstrated glial response to injury in addition to severe axonal pathology. Intriguingly, APP KO mice exhibited significant compensation of APP deficiency by other APP family proteins (APLP1, APLP2) in response to TBI. Axonal pathology findings observed in the mouse model of TBI are currently being replicated using human stem cell derived neurons in a unique cell culture TBI paradigm. In summary, we here used mouse and cell culture models of TBI in an APP deficient setting to uncover novel behavioral and immunohistochemical phenotypes, which further our understanding of APP in TBI, CTE and AD.

Disclosures: K. Texlová: None. **B.P. Head:** None. **V. Pozo Devoto:** None. **M. Novaková:** None. **M. Feole:** None. **G. Stokin:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.18/Z17

Topic: C.10. Brain Injury and Trauma

Support: Institutional Development Award (IDeA) from the NIGMS of the NIH grant P20GM103449.

Title: Genetic analysis of anxiety behavior following mild traumatic brain injury in *Drosophila melanogaster*

Authors: G. FORT[1], M. CHAMPAGNE[1], R. K. KELLY[1], D. MORAN[1], J. MARRIOTT[2], *A. CROCKER[2]
[2]Neurosci. Program, [1]Middlebury Col., Middlebury, VT

Abstract: Traumatic brain injuries (TBIs) contribute to increased mortality and permanent disability in the United States each year. While the effects of a major TBI are well appreciated, the effects of repeated mild TBI are only now becoming apparent. The acute and long-term consequences of mild TBI can include impaired memory, impaired movement, sleep patterns, and emotional functioning, such as anxiety and stress responses. In humans we see variations in how mTBI manifests itself both acutely and over the long term. In the fruit fly, *Drosophila melanogaster,* we also see natural variation in lifespan and sleep following mTBI. In addition, flies possess an ancient anxiety pathway which is activated following heat stress and visualized through wall-following and aggregation. This allows us to explore how mTBI alters the anxiety response in a genetically tractable organism (the fruit fly). In this pilot project we hypothesize that natural variation in mTBI anxiety behavior is driven by genetic variation in fly populations. Specifically the idea that genetic variants of small effect contribute additively to the expression of anxiety behavior. To test this we used a subset of 37 inbred fly lines of the *Drosophila* Genetic Reference Panel (DGRP), to explore the anxiety responses following mTBI. The DGRP allow us to use whole genome association mapping of loci associated with the quantitative traits being studied. This pilot study looked at 3 biological replicates of 4 conditions (mTBI + heat stress, no mTBI + heat stress, mTBI + no heat stress, no mTBI+no heat stress) for each line. This pilot project sought to establish anxiety and mTBI as a quantitative trait and examine preliminary differences in populations in anxiety, motor (negative geotaxis) and mortality rate. To quantify anxiety the following data was collected: wall-following, speed of ambulation, distance traveled in arena, number of fly interactions, and distance between flies within arena. We recorded behavior from more than 1500 animals and scored them for behavior using Noldus Ethovision software. Preliminarily, we see differences in aggregation and wall-following, suggesting that these behaviors possess genetic components influencing their differential expression between lines. In parallel to this study, we also collected whole brain RNAseq data from CantonS flies following heat stress and mTBI. Preliminary data suggests that neuropeptide like protein 4 (Nplp4) may be playing a role in anxiety behavior. Further work in this study will focus on extending phenotypic classification to all the DGRP lines as well as genetic analysis of potential association loci and coupling this with the whole brain RNAseq dataset.

Disclosures: G. Fort: None. **M. Champagne:** None. **R.K. Kelly:** None. **D. Moran:** None. **J. Marriott:** None. **A. Crocker:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.19/Z18

Topic: C.10. Brain Injury and Trauma

Support: CAPES

Title: The influence of a nematode parasite on host serotonergic system

Authors: *D. M. ZANCAN[1], C. V. MACHADO[2], F. J. V. FUENTEALBA[2], F. C. NICOLA[2]
[1]Physiol. Dept., [2]Neurosci. Grad. Program, Univ. Federal Do Rio Grande Do Sul (UFRGS), Porto Alegre, Brazil

Abstract: Mollusks are often involved in parasite life cycles as intermediate hosts. The parasites with such life cycle usually adopt strategies to facilitate its transmitting to the definitive host. To reach this target, the parasites can cause morphologic, metabolic, and immune alterations in different organs, including the nervous system of the intermediate hosts. This study aims at evaluating whether the parasite load (*Strongyluris* sp.) and the presence of the parasitic cysts in the nervous system of the *Megalobulimus abbreviatus* modifies the serotonin level in different lobes of cerebral ganglia (CG). Adult snails were collected from two areas of 90 m apart (Barra do Ribeiro, RS, Brazil), where the animals show distinct behaviors: in the first site the snails were in a shaded area and buried, while in the site 2 they were unearthed and in a high population density. The parasite load and the 5HT immunoreactivity (ir) were compared between these two sites. The optic densitometry (O.D.) were carried out. The 5HT-ir was also analyzed among three animal groups (G, n=24), constituted as follows: absence of cysts in the central nervous ganglia (G1), animals with cysts in the suboesophageal ganglia (SUBG, G2), and cysts in both CG and SUBG (G3). The values of O.D. of 5HT-ir from different lobes of CG were analyzed with one-way ANOVA (between G1, G2, G3). The correlation coefficient (Pearson's r) between the number of cysts in animals and the O.D. of 5HT-ir from different regions of CG was performed. Differences between the mean number of cysts and the O.D. from animals of each collection site were analyzed by Student's t test ($p<0,5$). The O.D. of 5HT-ir of all the animals showed significant negative correlation with the number of parasite cysts in snails ($r=-0,83$). Both the mesocerebrum, which regulates feeding behavior in all studied pulmonate gastropod mollusks, and the procerebrum, which is thought as an associative sensorial area, showed lower means of 5-HT-ir O.D. in G3 in comparison to G1 and G2 ($p=0,017$ and $p=0,06$). The medium region of CG, through which the pathways of those lobes project towards the SUBG, showed decrease of 5HT-ir, which has significant negative correlation with the number of cysts in all the animals ($r=-0,87$). The presence of *Strongyluris* cysts in the CG of the *M. abbreviatus* leads to a

5HT-ir decrease in the medium regions of CG. However, the relationship between the decrease of 5HT-ir and the unusual behavior observed in field snails was not clear. A systematic laboratory study of the behavior of snails infected with *Strongyluris* is required. Support: CAPES

Disclosures: D.M. Zancan: None. **C.V. Machado:** None. **F.J.V. Fuentealba:** None. **F.C. Nicola:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.20/AA1

Topic: C.10. Brain Injury and Trauma

Support: BU Start-up Funds

Title: Chronic *in vivo* imaging of neurovascular changes in cortex following mild traumatic brain injury

Authors: *E. WITKOWSKI[1], E. ERDENER[2], K. KILIC[2], D. BOAS[2], I. DAVISON[1]
[1]Biol., [2]Biomed. Engin., Boston Univ., Boston, MA

Abstract: From war zones to athletics to everyday falls, traumatic brain injury (TBI) is increasingly recognized as a major health concern. However, there are still no effective treatments, largely due to lack of understanding about how TBI affects the brain during the minutes to hours after injury. To characterize the nature and time course of rapid TBI-induced damage *in vivo*, we used minimally invasive imaging methods to measure neural activity and cerebral blood flow (CBF) in mouse visual cortex in a closed-skull weight drop model of mild TBI. Chronic cranial windows allowed for repeated measurements at high temporal and spatial resolution. Multiphoton Ca^{2+} imaging revealed a dichotomy in effects on neural activity where most layer 2/3 excitatory cells had significantly reduced spontaneous activity compared to pre-injury levels, but a minority of the cells became hyperactivated and showed repetitive long-duration Ca^{2+} transients that appeared 30-60 minutes after mild TBI. These data indicate pronounced disruption of normal cortical function beginning immediately after injury, including prolonged rises in intracellular Ca^{2+} that may contribute to long-term pathology. Given the extremely high energetic demands of brain tissue and the tight coupling of neural and vascular function, we also examined corresponding changes in cerebral blood flow after mild TBI. We used laser speckle microscopy and optical coherence tomography to measure CBF *in vivo* throughout a large portion of the vascular tree at capillary-level resolution. Speckle data showed a ~40% drop in CBF in the superficial pial vessels, and tomography revealed a similar reduction in capillaries located ~250 um below the surface in layer 2/3 beginning within 20 minutes of

mild TBI. Capillary-level changes were due to a striking increase in extended 'flow stalls' on the day of injury. The majority of CBF recovered within 2-3 hours, though some animals showed reduced flow lasting at least 3 days. The pronounced, long-lasting decrease in CBF is likely to cause energetic stress that may further contribute to eventual neuropathology. Future experiments will examine the causal relationship between effects on neural activity and CBF after mild TBI, providing valuable insight into what changes are occurring and when, both of which are critical for developing new treatment strategies.

Disclosures: E. Witkowski: None. **E. Erdener:** None. **K. Kilic:** None. **D. Boas:** None. **I. Davison:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.21/AA2

Topic: C.10. Brain Injury and Trauma

Support: DA-PRMRP W81XWH-16-1-0166

Title: Glial immune-related pathways as mediators of closed head TBI effects on behavior in *Drosophila*

Authors: *B. VAN ALPHEN[1], S. STEWART[4], M. IWANASZKO[2], A. RAMAKRISHNAN[1], T. Q. ITOH[5], R. ALLADA[3]
[1]Dept. of Neurobio., Northwestern Univ., Evanston, IL; [2]Dept. of preventive Med., Northwestern Univ., Chicago, IL; [3]Neurobio., Northwestern Univ., Evanston, IL; [4]Dept of Neurosci., Baylor Col. of Med., Houston, TX; [5]Fac. of Arts and Sci., Kyushu Univ., Fukuoka, Japan

Abstract: In Traumatic Brain Injury (TBI) the initial injury phase is followed by a secondary phase as inflammatory events in the brain contribute to widespread cell death and neurodegeneration. To study the mechanisms that mediate TBI pathology, we developed a Drosophila head-specific model for TBI, where well-controlled, non-penetrating strikes are delivered to unanesthetized flies. This assay recapitulates many TBI phenotypes, including increased mortality, impaired motor control, impaired sleep, and increased neuronal cell death. We detect a strong sterile immune response as genes involved in innate immunity are transiently up-regulated 24 hours after TBI, including those involved in proteolysis and activation of antibacterial, antifungal and antiviral defense responses as well as activation of apoptotic, autophagic and phagocytotic pathways. TBI-dependent behavioral changes are dependent on the master immune regulator NF-KB. These studies validate a new model for TBI in Drosophila and

identify glial immune pathways as candidate mediators of TBI effects. This study is funded by a Discovery Award from the Peer Reviewed Medical Research Program (W81XWH-16-1-0166)

Disclosures: B. Van Alphen: None. **S. Stewart:** None. **M. Iwanaszko:** None. **A. Ramakrishnan:** None. **T.Q. Itoh:** None. **R. Allada:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.22/AA3

Topic: C.10. Brain Injury and Trauma

Support: UBACYT Grant 20020160100005BA

Title: Noise exposure at different developmental ages can induce different short and long term habituation memory alterations. Correlation with hippocampal oxidative state

Authors: S. J. MOLINA[1], M. RODRIGUEZ GONZÁLEZ[2], G. E. BUJÁN[2], F. CAPANI[3], *L. R. GUELMAN[2,4]
[1]Consejo Nacional de Inv. Científicas y Técnicas. Univ. de Buenos Aires, CEFYBO (UBA-CONICET), Buenos Aires, Argentina; [2]Univ. De Buenos Aires, Facultad De Medicina, Buenos Aires, Argentina; [3]Inst. Inv. Cardiológicas, ININCA (UBA-CONICET), Buenos Aires, Argentina; [4]CEFyBO (UBA-CONICET), Buenos Aires, Argentina

Abstract: We have previously shown that exposure of immature rats to moderate noise levels was able to induce hippocampus (HC)-related behavioral and molecular alterations during the peri-adolescence period. The housing of these animals in an enriched environment (EE) reversed most of these alterations. However, comparative data of behavioral performances between animals evaluated at different intervals post-training (short and long-term) was not obtained yet.Thus, the aim of the present work was to test behavioral parameters of rats exposed to noise at two early developmental ages and at different intervals post training in an open field device (OF), as well as to evaluate a potential correlation with differences in HC oxidative markers (thioredoxins Trx1 and Trx2). In addition, housing in an EE was also studied to evaluate the possible reversal of these changes.Male Wistar rats of 7 and 15 days of age (N7 and N15) were exposed to noise (95-97 dB) for 2 hours. After weaning, rats were transferred to an EE, consisting of toys, a wheel, plastic tunnels and ramps, whereas others were placed in standard cages. After one week, OF task was performed to evaluate short and long-term habituation memory and the levels of Trx1and Trx2 were tested through Western blot experiments. Results showed no differences in short-term memory of N7 rats and a decrease in long-term memory when compared to control group. On the contrary, N15 animals showed a decrease in short-term

memory without significant changes in long-term memory. Interestingly, short and long-term alterations were fully prevented when animals were housed in EE. Furthermore, western blot experiments showed that N7 and N15 rats had an increase in hippocampal Trx1 levels that was reversed when animals were housed in EE. Finally, no significant changes were observed in Trx2 levels in either group.In conclusion, these findings suggest that rats exposed to noise at different developmental ages might be differentially affected in their behavioral performance. On the other hand, Trx1 seemed to be more sensitive to the effects of noise exposure than Trx2. As differences between behavioral performances were observed but similar results in Trx1and Trx2 levels were found among groups, it could be suggested that these parameters do not seem to be correlated. Moreover, EE was an effective strategy to reverse all the behavioral and molecular alterations found in both groups, suggesting that visual, social and physical stimulation during the peri-adolescence period could be an effective strategy to reverse HC-related behavioral and molecular changes.

Disclosures: S.J. Molina: None. **M. Rodriguez González:** None. **G.E. Buján:** None. **F. Capani:** None. **L.R. Guelman:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.23/AA4

Topic: C.10. Brain Injury and Trauma

Support: NIH R01DC012060 (HZ)
R01DC014930 (WZ)
R21EY025550 (WZ)
CPN animal behavioral core P30GM10332

Title: A novel animal model of blast-induced traumatic brain injury (TBI)

Authors: J. LI[1,2], N. LI[2], L. WU[2], Y. PANG[3], T. CHEN[1], Y. OU[1], Y. TU[1], D. SANDLIN[1], J. P. SHAFFERY[4], *H. ZHU[1], W. ZHOU[1]
[1]Univ. MS Med. Ctr. Dept ENT, Jackson, MS; [2]Kun Ming Med. Sch., Kun Ming, China; [3]Univ. of Mississippi Med. Ctr. / Dept of Pediatrics, Jackson, MS; [4]Univ. Mississippi Med. Ctr. Dept Psychiatry, Jackson, MS

Abstract: Exposure to blast shockwave often leads to traumatic brain injury (TBI) in military and civilian populations. As air-filled structures and directly exposed to the surrounding air, the unprotected ears are among the most frequently damaged sites during blast exposure. Moreover, a previous study revealed a significant association between tympanic membrane perforation and

traumatic brain injury in victims of blast exposure (Xydakis et al., 2007). However, little is known about how and the extent to which blast energy impacts the central nervous system via the external ear canal. To fill this important knowledge gap, we developed a novel model showing that exposure to a single blast shockwave delivered into the external ear canal caused brain injuries in rats. Adult female Long-Evans rats were anesthetized and exposed to a single blast of 40PSI (275kPa, 80% of the lethal intensity determined in Sandlin et al., 2018) or 0PSI (sham condition) delivered to the left ear. Brain tissues were harvested for histology at 6 hours, 1, 3, 7, 14, 30 and 60 days after blast exposure. Preliminary immunohistochemistry data showed an extensive activation of microglia, demonstrated by a significant increase in IBa1+ cells with activated morphology, in the brain stem regions ipsilateral to the blasted ear. Caspase-3 and NeuN double-immunostained cells were also detected in these regions, indicating blast-induced neuron death. Open field tests further showed that the blasted rats exhibited signs of anxiety compared to rats in the sham condition. These results suggested that blast shockwave via the ear canal not only damages the inner ear hair cells as we showed previously, but also causes injuries in the brain. Ongoing studies will further characterize the biomarkers of the blast-induced TBI and investigate the underlying mechanisms for developing prevention and treatment countermeasures. (T.L., N.L and L.W. made equal contribution)

Disclosures: J. Li: None. **N. Li:** None. **L. Wu:** None. **Y. Pang:** None. **T. Chen:** None. **Y. Ou:** None. **Y. Tu:** None. **D. Sandlin:** None. **J.P. Shaffery:** None. **H. Zhu:** None. **W. Zhou:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.24/AA5

Topic: C.10. Brain Injury and Trauma

Support: Chaire Fondation Caroline Durand en traumatologie aigüe de l'UdeM

Title: A combined rat model of mild traumatic brain injury and cerebral microdialysis

Authors: *I. O. MASSE[1], L. MOQUIN[3], C. PROVOST[2], A. P. GRATTON[3], L. DE BEAUMONT[2]
[1]Ctr. d'Etudes Avancées en Médecine du Sommeil, Hôpital Du Sacré-Cœur De Montréal, Montréal, QC, Canada; [2]Hôpital Du Sacré-Cœur De Montréal, Montreal, QC, Canada; [3]Douglas Hosp. Res. Ctr., Verdun, QC, Canada

Abstract: Mild traumatic brain injury (mTBI) represents a major public health concern due to persistent behavioral and neurological effects. The mechanisms by which mTBI lead to such effects are largely attributable to an hyperacute indiscriminate glutamate release. Cerebral

microdialysis studies in rodents reported a peak of extracellular glutamate 5 minutes after injury. Microdialysis has the advantage of being one of the few techniques allowing the quantification of neurotransmitters *in vivo* and at different time points following injury without sacrificing the animal. In addition to such techniques, translational animal injury models are needed to better understand the effects of mTBI. The Wayne State weight drop model allows the induction of an impact on the skull of a subject unrestrained by the fall of a weight, which allows rapid acceleration and deceleration of the head and torso, an essential feature in human craniocerebral trauma and a factor that is missing from other existing animal mTBI models. The aim of our study was to develop a rat model of mTBI, based on the Wayne State model, which incorporates the microdialysis technique to study extracellular glutamate changes over time *in vivo* following a mTBI. Glutamate was harvested from the extracellular fluid (ECF) using microdialysis before and after a trauma inflicted by the Wayne State model or sham and analyzed by high-performance liquid chromatography. The measurements were performed in the hippocampus as this region contains a high density of glutamatergic receptors making it vulnerable to the excitotoxicity generated by the glutamate release. Brains were harvested following mTBI or sham and processed for histological verification of probe placement and injury. ECF glutamate concentrations in the rat hippocampus were increased immediately after mTBI as compared with the sham procedure. Our modified weight drop model thus induced changes in ECF glutamate concentrations that are representative of the peak previously reported. Given the simplistic nature of the Wayne State model, and the relevant ECF glutamate concentration changes measured using microdialysis, this combined rat model of mTBI and microdialysis could provide researchers with a reliable and translational model of mTBI that could be used in a wide variety of therapeutical studies.

Disclosures: I.O. Masse: None. **L. Moquin:** None. **C. Provost:** None. **A.P. Gratton:** None. **L. De Beaumont:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.25/AA6

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant 1S10OD021598
University of New Mexico Brain and Behavioral Health Institute
Child Health Signature Program
Dedicated health research funds from the University of New Mexico

Title: Microstructural and ultrastructural brain injury in a preclinical model of acquired symptomatic hydrocephalus: Exploring the spectrum of cilia injury

Authors: *T. R. YELLOWHAIR[1], J. NEWVILLE[1], C. SHROCK[2], J. MAXWELL[3], S. ROBINSON[4], L. JANTZIE[1]
[1]Dept. of Pediatrics and Neurosciences, Univ. of New Mexico Sch. of Med., Albuquerque, NM; [2]Johns Hopkins Sch. of Med., Baltimore, MD; [3]Univ. of New Mexico Hosp., Albuquerque, NM; [4]Neurosurg., Johns Hopkins Univ., Baltimore, MD

Abstract: Acquired symptomatic hydrocephalus (ASH), typically marked by ventriculomegaly and elevated intracranial pressure, is a serious problem worldwide. Currently, the only treatment available for ASH is surgical intervention to divert cerebrospinal fluid, and many people with ASH do not have access to safe and timely neurosurgery. Shunts, the most common intervention, are prone to malfunction and infection. Clinical studies suggest a strong correlation between systemic inflammation and the propensity for ASH in the setting of hemorrhagic brain injury. To facilitate improved understanding of the pathophysiology of ASH in the context of intraventricular hemorrhage (IVH) and systemic inflammation, we created a novel preclinical model. We tested the hypothesis that IVH plus systemic inflammation would induce ventriculomegaly, injury to ependymal motile cilia (EMC) and result in multiple diffusion tensor imaging (DTI) abnormalities. On postnatal days 21 (P21) and P23, Sprague Dawley rats received an intraperitoneal injection of 3mg/kg lipopolysaccharide (LPS) or saline. On P25, under anesthesia, rats received a bilateral intraventricular injection of either 50µl lysed littermate red blood cells (IVH) or phosphate buffered saline (PBS). On P45 rats were sedated and perfused for *ex vivo* magnetic resonance imaging (MRI) (n=3-6/group) on a Bruker 7T BioSpec 70/30 Ultra Shield Refrigerated nuclear system or for scanning electron microscopy (SEM) using a Zeiss Sigma 300 field scanning electron microscope. Ventricular volume was calculated on T2 structural imaging and fractional anisotropy (FA) analyzed in the corpus callosum on DTI. Group differences were compared with a Student's t-test with $p<0.05$ indicating statistical significance. Compared to saline-PBS treated rats, LPS-IVH rats have significantly reduced FA in the corpus callosum ($p=0.0003$) consistent with microstructural white matter injury and reduced anatomical connectivity. LPS-IVH rats also have significantly larger ventricular volumes than saline-PBS rats ($p=0.01$). SEM revealed LPS-IVH rats have denudated, matted, and patchy EMC compared to saline-PBS rats. Taken together, these data support the hypothesis of widespread structural abnormalities and ventriculomegaly in a novel rat model of ASH. Further stratification of the brain injury associated with ASH is necessary to facilitate the development of less invasive therapeutic strategies, and to improve long-term outcomes for people with ASH.

Disclosures: J. Newville: None. **C. Shrock:** None. **J. Maxwell:** None. **S. Robinson:** None. **L. Jantzie:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.26/AA7

Topic: C.10. Brain Injury and Trauma

Title: Neonatal erythropoietin and melatonin as non-surgical combination therapy prevents posthemorrhagic hydrocephalus of prematurity in rats

Authors: *C. L. SHROCK[1], T. R. YELLOWHAIR[2], J. C. NEWVILLE[2], F. S. CONTEH[1], A. Y. OPPONG[1], J. R. MAXWELL[2], F. J. NORTHINGTON[3], L. L. JANTZIE[2], S. ROBINSON[1]
[1]Neurosurg., Johns Hopkins Univ., Baltimore, MD; [2]Pediatrics and Neurosciences, Univ. of New Mexico, Albuquerque, NM; [3]Pediatrics and Neonatalogy, Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Posthemorrhagic hydrocephalus of prematurity (PHHP) is a serious global problem. When available, surgery, the only treatment, has limited long-term success. A safe, effective nonsurgical therapy is needed. Very preterm infants are prone to intraventricular hemorrhage (IVH), particularly when exposed to chorioamnionitis (CAM). Erythropoietin (EPO) and melatonin (MLT) are safe, endogenous cytokines currently in separate neonatal clinical trials. Using our rat PHHP model we hypothesized that combined EPO and MLT can prevent progressive macrocephaly (PMC) and ventriculomegaly (VM), phenotypic hallmarks of PHHP. The transcription factor yes-associated protein (YAP) promotes specification of radial glial cells into ependymal cells. We hypothesized that systemic inflammation lowers YAP and hinders radial glial cell differentiation into ependymal cells, contributing to PHHP. Pregnant rats underwent laparotomy on embryonic day 18 with transient uterine artery occlusion for 60 min and intra-amniotic sac lipopolysaccharide injection. Shams underwent laparotomy for 60 min. On postnatal day 1 (P1), CAM and sham pups were randomized to IVH (bilateral injection of littermate lysed red blood cells) or sterile vehicle (veh, phosphate buffer saline) injection. On P2, CAM-IVH pups were randomized to EPO (2000U/kg ip P2-5, P7, and P9) plus MLT (20 mg/kg ip P2-P10) or vehicle. Rats were coded, and observers were blinded to group. Daily intra-aural distance (IAD) was measured as a surrogate for head circumference, and neurodevelopmental testing was performed. Ventricular volumes and microstructural abnormalities were analyzed with *ex vivo* MRI at P21. qPCR was used to quantify P15 YAP mRNA levels. Significance was calculated with two-way ANOVA with Bonferroni correction, and Wilcoxon rank sum, with $p<0.05$ significant. Neonatal EPO+MLT prevented macrocephaly and mitigated developmental delay in treated CAM-IVH rats, compared to vehicle-treated CAM-IVH rats (n=17-24, p=0.026). EPO+MLT treatment also significantly reduced P21 VM on MRI (Wilcoxon rank sum test, p=0.005). Reduction of YAP mRNA levels occurred in vehicle-treated CAM-IVH rats (n=4),

compared to shams (n=7, p=<0.001) and EPO+MLT treated CAM-IVH rats (n=5, p=0.036), suggesting that EPO+MLT prevents YAP loss. Diffusion tensor imaging (DTI) showed that vehicle-treated CAM-IVH rats had widespread loss of microstructural integrity which was prevented with EPO+MLT (all p<0.05). These results suggest that sustained, systemic, combined neonatal EPO and MLT treatment prevents multiple hallmarks of PHHP, consistent with a clinically-viable, non-surgical treatment strategy.

Disclosures: C.L. Shrock: None. **T.R. Yellowhair:** None. **J.C. Newville:** None. **F.S. Conteh:** None. **A.Y. Oppong:** None. **J.R. Maxwell:** None. **F.J. Northington:** None. **L.L. Jantzie:** None. **S. Robinson:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.27/AA8

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NINDS R01NS091222

Title: Long term neuromodulation after experimental TBI results in rebound hyperexcitability indicated by enhanced fMRI activation and altered functional connectivity

Authors: *A. PAYDAR, J. S. SCHOENFIELD, E. YAN, A. KAMALI, T. KOCHAN, N. G. HARRIS
UCLA, Dept. of Neurosurgery, BIRC, Los Angeles, CA

Abstract: Functional disconnection and hyperconnectivity occur after traumatic brain injury, both clinically and in the rat model of CCI injury. We hypothesize that homotopic, cortical regions remote from the primary injury site develop hyperexcitability after injury, resulting in increased trans-hemispheric inhibition that prevents reorganization of the primary, injured hemisphere. This is supported by the finding that recovery of affected forelimb function can occur from early but not delayed temporary silencing of the contralesional cortex. To determine the effect of long term silencing of contralesional cortex on reorganization of brain circuits, we acquired forelimb-evoked-fMRI and resting state fMRI at 4 and 8wks post-injury after continuous intracortical infusion of muscimol into the contralesional, sensory-motor cortex homotopic to the primary injury site for 4 wks immediately following CCI injury and compared the data to vehicle-infused, injured (n=6 vs 5) and sham rats (n=2).Data were analyzed for forelimb-evoked brain activation and for network-based functional connectivity (fc). Despite recording a detrimental effect of muscimol on limb function opposite the muscimol-injected cortex at 7 days post-injury using a ladder behavioral task (indicating brain silencing), evoked

activation from the same forelimb 3wks later indicated the development of significant hyperexcitability (P&lt0.001, z&gt2.3 cluster-corrected), but not at 8wks post injury, 4wks following the removal of muscimol. There was no change in brain activation within the ipsilesional hemisphere evoked by the injury-affected limb at either time-point, indicating that the period of silencing was not long enough to enhance injured brain function, and/or the subsequent rebalancing of function toward hyperexcitation nulled any potentially positive effects. Hyperexcitability after TBI is likely to impact neural circuit and therefore we next determined the network topography that characterized the muscimol-induced hyperexcitability toward providing a network level understanding of TBI-induced hyperexcitability. We found a decrease in fc bilateral within and between the cortical hemispheres 4wks after chronic muscimol infusion, indicating cortical isolation (P&lt0.05, FDR-corrected q=0.05). This was accompanied by a significant, bilateral increase in cross-brain, cortico-subcortical fc, possibly indicating circuit-level refinement consistent with the enhanced evoked activation of the muscimol-affected limb. Data indicate that chronic neuromodulation after TBI may result in complex temporal effects, and that shorter periods may be more optimal.

Disclosures: A. Paydar: None. **J.S. Schoenfield:** None. **E. Yan:** None. **A. Kamali:** None. **T. Kochan:** None. **N.G. Harris:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.28/AA9

Topic: C.10. Brain Injury and Trauma

Title: Quantitative measurement of CBV in mild traumatic brain injury using MRI

Authors: *J. QIAO[1], T. MORRISON[2], A. MALLETTE[3], L. TIMMS[4], P. P. KULKARNI[7], S. KAMARTHI[5], C. F. FERRIS[8], S. SRIDHAR[6]
[1]Dept. of Mechanical and Industrial Engin., [2]Psychology, [3]Neurosci., [4]Physics, [5]Mechanical and Industrial Engin., [6]Dept. of Physics, Northeastern Univ., Boston, MA; [7]Psychology, Northeastern Univ. Dept. of Psychology, Boston, MA; [8]Psychology, Northeastern University, Ctr. for Translational NeuroImaging, Boston, MA

Abstract: Traumatic brain injury is one of the most prevalent risks of death and disability in young people, with about 1.6 million reported per year in the US. Some of the most devastating injuries from brain trauma are the rupturing of arteries between the dura and the skull in an epidural hematoma, as well as tears in emissary veins, resulting in hemorrhagic contusions seen in subdural hematomas. This accumulation of blood can squeeze and increase pressure on the brain. TBI can also cause structural and neurological damage, often seen in athletes who suffer

repeated injury. Here, we introduce a novel application of our previously developed imaging modality, quantitative ultra-short time-to-echo contrast-enhanced (QUTE-CE) MRI using FDA-approved superaramagnetic iron oxide nanoparticle (SPION) ferumoxytol to image blood accumulation and to detect cerebral blood volume (CBV) changes in mild TBI animals. Sprague Dawley rats were divided into two groups: control group and TBI group which received 3 mild hits for 3 continuous days. Rats in TBI group underwent QUTE-CE MRI before mild hit and immediately after each hit for 1.5 hours while control group underwent the same imaging sessions without traumatic brain injury. Quantitative global CBV map and regional CBV were calculated from QUTE-CE MRI and a 174-region rat brain atlas. This study demonstrates that QUTE-CE MRI is sensitive to detect CBV changes in mild TBI rats.
Conflict of interest QUTE-CE MRI is the subject of a patent application assigned toNortheastern University (inventors Codi A. Gharagouzloo and SrinivasSridhar).

Disclosures: J. Qiao: None. **T. Morrison:** None. **A. Mallette:** None. **L. Timms:** None. **P.P. Kulkarni:** None. **S. Kamarthi:** None. **C.F. Ferris:** None. **S. Sridhar:** None.

Poster

663. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 663.29/AA10

Topic: C.10. Brain Injury and Trauma

Title: Traumatic brain injury: Characterization of a cryoinjury model using MRI and histopathology

Authors: *V. SHENOY[1], H. BATTAPADY[1], L. LOOSE[1], S. JOHNSON[1], D. LOSE[1], P. HARRIS[1], S. LUNN[1], B. D. TRAPP[2]
[1]Renovo Neural, Cleveland, OH; [2]Cleveland Clin. Fndtn, Cleveland, OH

Abstract: Traumatic brain injury (TBI) elicits an inflammatory response in the CNS that involves both resident and peripheral immune cells. In this pilot study, we characterize a cryoinjury animal model of TBI using MRI and histopathology, to study its pathogenesis and recovery.
10-week-old C57Bl/6J mice were used for cryoinjury. Cryoinjury was performed as described previously. Previous studies have shown inhibition of erythropoietin (EPO) activity worsens severity of neuronal injury, suggesting its involvement in an intrinsic neuronal repair pathway. Study groups: TBI only (n=3), TBI+EPO (n=3). A separate cohort of n=3 mice were used to study reproducibility of cryoinjury procedure. rhEPO at a dose of 5000 U/kg body weight was administered IP at 6 hours and at 3 and 7 days(d) after cryoinjury TBI. 2D MR images were acquired on a 7T Bruker-Biospec MRI at 1d, 2d, 3d, and 6d post injury. T2w MRI to quantify

total brain volume and abnormal volume (AV) (segmented into 2 categories: “hypo-intense”(HypoBV) and “hyper-intense”(HypreAV)) due to TBI; Brains from TBI animals perfused at day 3 post-TBI were embedded in paraffin. LFB staining was used to delineate lesion boundaries, adjacent Iba1-stained sections were used to quantify area covered by microglia, neuronal cell loss and degeration was quantified using NeuN stain and silver stain respectively. Cryoinjury model of TBI in mice shows high reproducibility in achieving consistent focal cortical lesions with a 100% survival rate. MRI can detect the timeline for recovery after cryoinjury, day 1 through day 6. By day 6 total abnormal MRI volume is reduced by 66% compared to day 1. EPO treatment reduces AV in mice after TBI compared to TBI only controls, with maximum reduction of 10% seen in EPO group at day 3 post TBI. HypoAV is consistently higher in EPO treated animals. HyperAV is reduced in the EPO group compared to TBI only control, with a maximum reduction of 25% seen at day3. HyperAV may be suggestive of inflammation and edema in this region. The area covered by IBA1 positive microglia in peri-lesion area ipsilateral to TBI in the cortex of EPO treated mice is significantly increased by 17% ($p<0.01$) compared to the contralateral control side and by 25% ($p<0.003$) compared to TBI only control group. Although we see a reduction in hyperAV in the EPO treated animals, there is an increase in IBA1 positive microglia cells in the peri-lesion region as shown by histology. This therapeutic significance of EPO may suggest neuroprotective functions of the microglia. These results suggest that this mouse cryoinjury model and the MRI and histopathology metrics can be a valuable tool for pre-clinical assessment of drugs to treat Traumatic Brain Injury.

Disclosures: H. Battapady: A. Employment/Salary (full or part-time):; Renovo Neural, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Renovo Neural, Inc. **L. Loose:** A. Employment/Salary (full or part-time):; Renovo Neural, Inc. **S. Johnson:** A. Employment/Salary (full or part-time):; Renovo Neural Inc. **D. Lose:** A. Employment/Salary (full or part-time):; Renovo Neural Inc. **P. Harris:** A. Employment/Salary (full or part-time):; Renovo Neural Inc. **S. Lunn:** A. Employment/Salary (full or part-time):; Renovo Neural Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Renovo Neural Inc. **B.D. Trapp:** A. Employment/Salary (full or part-time):; Cleveland Clinic. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Renovo Neural Inc..

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.01/AA11

Topic: C.10. Brain Injury and Trauma

Support: Academy of Finland
Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital
The Finnish Medical Foundation
Orion Research Foundation
The Paulo Foundation

Title: Increased rightward frontal alpha asymmetry after mild traumatic brain injury

Authors: *V. KUUSINEN[1,2], L. SUN[1,3], J. PERÄKYLÄ[1,2], K. H. OGAWA[4], K. M. HARTIKAINEN[1,2]
[1]Behavioral Neurol. Res. Unit, Tampere, Finland; [2]Fac. of Med. and Life Sci., Univ. of Tampere, Tampere, Finland; [3]Turku PET Ctr., Turku, Finland; [4]Dept. of Psychology, St. Mary's Col. of California, Moraga, CA

Abstract: Frontal rightward EEG alpha asymmetry (FAA) has been linked with depression or vulnerability to it (Thibodeau et al., 2006). Some patients with mild traumatic brain injury (mTBI) suffer from prolonged post-concussion symptoms, including depressive symptoms. In line with potential vulnerability to depression, we previously reported increased attention to threat-related emotional stimuli in subjects with history of mTBI (Mäki-Marttunen et al., 2015). In this exploratory study, we investigated whether patients with previous mTBI would show increased FAA.
We studied 26 patients (14 males, 12 females, mean age = 40.5 years) with previous mTBI who were on average 20 months post-injury and 17 control subjects (7 males, 10 females, mean age = 40.3 years) with no history of head injury. The mTBI group was further divided into symptomatic (n = 14, still reporting any post-concussion related symptoms) and non-symptomatic (n = 12) groups based on the Rivermead Post-Concussion Symptoms Questionnaire (King et al., 1995). Depressive symptoms were also assessed using the Beck Depression Inventory (Beck et al., 1996). Participants performed a computer-based executive function task containing emotional stimuli, i.e. Executive-reaction time test, while their EEG was recorded. Both task-related FAA and task-performance were assessed.
The mTBI group showed significantly increased frontal alpha asymmetry compared to the control group. Excluding participants with depressive symptoms did not change the result. When mTBI group was divided into symptomatic and non-symptomatic subgroups and compared to Controls, group difference in alpha asymmetry was close to significance ($p = 0.053$), but post-hoc tests yielded no further significance. There was also a Group x Emotion interaction, where post-hoc analysis showed increased FAA in context of emotional stimuli in symptomatic mTBI group and in context of neutral stimuli in non-symptomatic mTBI group. No effect of emotional stimuli on alpha asymmetry was seen in Controls. No differences in cognitive performance were observed between groups.
In conclusion, we detected increased rightward frontal alpha asymmetry in patients with previous mild traumatic brain injury. Pronounced alpha asymmetry in context of emotional stimuli in symptomatic mTBI patients may reflect increased tendency to process negative emotion, which may further predispose to emotional symptoms, like depression. FAA during a cognitive task

with threat-related stimuli has been suggested to reflect impact of neuromodulation on limbic circuitries (Sun et al., 2017) and may well have potential as a biomarker of altered emotional processing after mTBI.

Disclosures: V. Kuusinen: None. **L. Sun:** None. **J. Peräkylä:** None. **K.H. Ogawa:** None. **K.M. Hartikainen:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.02/BB1

Topic: C.10. Brain Injury and Trauma

Title: Investigation of the relationship of vocal-biomarker features and fMRI ROI time-series for the diagnosis of traumatic brain injury (TBI) in humans

Authors: *D. E. STURIM, J. WILLIAMSON, G. CICCARELLI, Y. GWON, 0242, T. QUATIERI
MIT Lincoln Lab., Lexington, MA

Abstract: In this work, we investigate the relationship between vocal eigen-features and the fMRI time-series of the BOLD response in regions of interest (ROI). We examine correlations between vocal features and the fMRI ROI time-series. Further investigation explores correlations between vocal features and the fMRI ROI to ROI connectivity measures. Initial results indicate relationships between vocal features and brain ROIs that may show which components of the neural speech networks effected by traumatic brain injury (TBI).
The data used for this study was collected by Purdue University on 32 high school athletes over the entirety of a sports season (Talavage, et al., 2014), and includes fMRI measurements made pre-season, in-season, and postseason. The athletes are 25 male football players and 7 female soccer players. The Immediate Post-Concussion Assessment and Cognitive Testing suite (ImPACT) was used as a means of assessing cognitive performance (Broglio, Ferrara, Macciocchi, Baumgartner, & Elliott, 2007). The test is made up of six sections, which measure verbal memory, visual memory, visual motor speed, reaction time, impulse control, and a total symptom composite. Using each test, a threshold is set for a change in cognitive performance. The threshold for each test is defined as a decline from baseline that exceeds one standard deviation, where the standard deviation is computed over the change from baseline across all subjects' test scores.
Time-series data are derived from resting state fMRI scans of the subjects. The pre-processing of the resting state fMRI and accompanying structural MRI data (for Atlas registration) was performed with the toolkit CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012). Functional connectivity was generated using cortical and sub-cortical atlas registrations.

Our results are showing relatively high correlations between the vocal features and three regions of the brain, 1) Inferior Frontal Gyrus pars triangularis, 2) Superior Temporal Gyrus posterior division and, 3) Supramarginal Gyrus posterior division.

*DISTRIBUTION STATEMENT (to be included after RR approval)
This material is based upon work supported by the Assistant Secretary of Defense for Research and Engineering under Air Force Contract No. FA8702-15-D-0001. Any opinions, findings, conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the Assistant Secretary of Defense for Research and Engineering.

Disclosures: D.E. Sturim: None. **J. Williamson:** None. **G. Ciccarelli:** None. **Y. Gwon:** None. **T. Quatieri:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.03/BB2

Topic: C.10. Brain Injury and Trauma

Support: EU grant H2020-FETOPEN-2014-2015-RIA n. 686764 “Luminous”
the EU grant H2020 grant agreement 720270-Human Brain Project SGA1

Title: Sleep-like bistability, loss of causality and complexity in the cerebral cortex of patients with unresponsive wakefulness syndrome

Authors: *M. FECCHIO[1], M. ROSANOVA[1], S. CASAROTTO[1], S. SARASSO[1], A. GIRARDI CASALI[2], A. PIGORINI[1], A. COMANDUCCI[1], F. SEREGNI[3], G. DEVALLE[4], G. CITERIO[5], O. BODART[6], O. GOSSERIES[6], M. BOLY[7], S. LAUREYS[6], M. MASSIMINI[1]
[1]Dept. of Biomed. and Clin. Sci. L.Sacco, Univ. of Milan, Milano, Italy; [2]Univ. Federal de São Paulo, Sao Jose dos Campos, Brazil; [3]Cambridge Univ. Hosp. NHS Fndn. Trust, Cambridge, United Kingdom; [4]IRCCS Fondazione Don Gnocchi Onlus, Milan, Italy; [5]Univ. of Milan Bicocca, Milan, Italy; [6]Univ. and Univ. Hosp. of Liège, Liege, Belgium; [7]Univ. of Wisconsin, Madison, WI

Abstract: INTRODUCTION In Unresponsive Wakefulness Syndrome (UWS) patients Transcranial Magnetic Stimulation (TMS) evokes an EEG potential (TEP) characterized by a sleep-like, positive-negative slow wave, a phenomenon previously observed during physiological non-rapid eye movement (NREM) sleep, in which cortical neurons become bistable and tend to fall into a silent OFF period upon receiving an input. Here we firstly test whether TEPs in UWS patients are characterized by the hallmarks of bistability. Then, we assess the hypothesis that the presence of OFF-periods may disrupt causality and complexity in the cortex of UWS patients by

means of the phase-locking factor (PLF) and the perturbational complexity index (PCI), respectively. METHODS TEPs were recorded in 16 UWS patients, in 20 awake healthy subjects and 8 during NREM sleep targeting frontal and parietal areas. To assess the presence of cortical OFF-periods we measured the amplitude of TEPs filtered below 4 Hz and the high frequency (>20 Hz) suppression by means of time-frequency spectra decomposition. PLF was calculated after filtering trials above 8 Hz. Last significant time point was considered assuming a Rayleigh distribution of the baseline values and setting the statistical threshold at $\alpha<0.05$. PCI were calculated applying the automatic procedure described in (casali, casarotto). Specifically, given the temporal evolution of PCI, we measured the first time point in which PCI reached its maximum. RESULTS TEPs recorded in UWS patients differed from the waveforms obtained in healthy wakefulness but were similar to the responses obtained in healthy subjects during NREM sleep, which are characterized by a large positive-negative deflection associated with a significant suppression of high-frequency EEG power, reflecting a cortical OFF-period. Moreover, compared to healthy wakefulness, TEPs recorded in UWS patients were characterized by an early drop of PLF below significance level. Slow-wave amplitude, suppression of high frequency power and phase-locking duration were significantly correlated. Considering the first time point in which PCI reached its maximum, we found that the build-up of complexity in UWS patients was significantly shorter (Wilcoxon ranksum test, $p<0.01$) than healthy awake subjects and was significantly correlated with the timing of the high frequency suppression and the phase-locking duration. CONCLUSIONS Our results suggest that the slow waves evoked by TMS in UWS patients may be the EEG reflection of a cortical OFF-period that disrupts deterministic activity patterns in response to a stimulus and the overall brain complexity, a key theoretical requirement for consciousness.

Disclosures: M. Fecchio: None. **M. Rosanova:** None. **S. Casarotto:** None. **S. Sarasso:** None. **A. Girardi Casali:** None. **A. Pigorini:** None. **A. Comanducci:** None. **F. Seregni:** None. **G. Devalle:** None. **G. Citerio:** None. **O. Bodart:** None. **O. Gosseries:** None. **M. Boly:** None. **S. Laureys:** None. **M. Massimini:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.04/BB3

Topic: C.10. Brain Injury and Trauma

Title: Elevated levels of BNDF, depression, anxiety, and stress following mild traumatic brain injury

Authors: *T. SUSA[1], R. BRANDT[2], K. J. KANGAS[2], C. BAMMERT[2], E. N. OTTEM[3], M. T. MOORE[4], J. M. CARLSON[5]

[1]Psychology/Neuroscience, [3]Biol., [4]Sch. of Hlth. and Human Performance, [5]Psychology, [2]Northern Michigan Univ., Marquette, MI

Abstract: Brain derived neurotrophic factor (BDNF) is an important protein involved in neuronal survival, synaptic plasticity, and stress reactivity. In particular, BDNF levels are heightened under conditions of stress and are altered following traumatic brain injury. BDNF levels can be reliably obtained in blood serum. Recently, it has been discovered that BDNF can also be measured in human (and non-human) saliva. However, the relationship between serum and salivary BDNF is poorly understood—especially in relation to alterations in BDNF levels following mild traumatic brain injury (mTBI). This study aimed to bridge this gap by collecting BDNF from both serum and saliva in a sample of 44 collegiate studente student athletes. Half of the participants (n = 22) were recently cleared to return to play after experiencing a sports-related concussion. The other half of participants (n = 22), had not experienced a concussion within the past year and were matched on age, sex, and sport. To assess participants' stress-related affective symptoms, the depression, anxiety, and stress survey (DASS) was administered. Saliva samples were collected using a passive drool method, 2-4 ml of saliva was collected per participant. Five ml blood samples were collected by a trained phlebotomist. All samples were aliquoted and centrifuged for their respective times and then stored at -80 degrees Celsius until further handling. BDNF levels were analyzed with a commercial ELISA kit in duplicate with standard curve R^2 values of .992, and .995 for the salivary and serum samples respectively. Levels of depression, anxiety, and stress were all elevated in the concussion, relative to the control, group. When controlling for these affective variables, serum BDNF was elevated in the concussion group. However, there was no difference in salivary BDNF when controlling for affective variables and time of sample. Furthermore, BDNF levels were not correlated across serum and saliva samples—suggesting that salivary BDNF is not a reliable substitute for serum BDNF. In sum, the results suggest that concussions are is associated with elevated levels of serum, but not salivary, BDNF as well as heightened levels of depression, anxiety, and stress.

Disclosures: T. Susa: None. **R. Brandt:** None. **K.J. Kangas:** None. **C. Bammert:** None. **E.N. Ottem:** None. **M.T. Moore:** None. **J.M. Carlson:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.05/BB4

Topic: C.10. Brain Injury and Trauma

Support: NIH RC2 NS069409
U01 NS08090
DoD W81XWH-14-2-0176

Title: Prognostic inflammatory biomarkers for traumatic brain injury: A TRACK-TBI pilot study

Authors: *M. HABER[1], J. PODDELL[3], F. KORLEY[4], D. WILSON[5], A. R. FERGUSON[6], P. MUKHERJEE[7], K. WANG[8], A. VALADKA[9], A. PUCCIO[10], D. OKONKWO[10], G. MANLEY[11], R. DIAZ-ARRASTIA[2]
[1]Neurol., [2]Dept Neurol., Univ. of Pennsylvania, Philadelphia, PA; [3]Univ. Of Pennsylvania, Philadelphia, PA; [4]Univ. of Michigan, Ann Arbor, MI; [5]Quanterix Corp., Boston, MA; [6]Dept. of Neurolog. Surgery, Brain and Spinal Injury Ctr. (BASIC), UCSF, San Francisco, CA; [7]Professor of Radiology & Bioengineering, Univ. of California San Francisco, San Francisco, CA; [8]Univ. of Florida, Gainesville, FL; [9]Virginia Commonwealth Univ., Richmond, VA; [10]Univ. of Pittsburgh, Pittsburgh, PA; [11]UCSF, San francisco, CA

Abstract: Clinical research and management of traumatic brain injury (TBI) would greatly benefit from the development of diagnostic and prognostic blood biomarkers. The FDA recently approved protein biomarkers for TBI (GFAP, UCHL1) as diagnostic biomarkers to aid in the evaluation of mild TBI, however, there are currently no prognostic biomarkers available. This study aimed to assess the prognostic potential of candidate brain injury markers (GFAP, UCHL1, NFL, Tau) and inflammatory cytokines (IL-6, IL-10, TNF-alpha) for outcome after TBI. Plasma blood samples were collected from TBI subjects enrolled in the TRACK-TBI Pilot Study at three Level I academic medical centers, within 24 hours of injury. Biomarker assays were performed on the SIMOA HD-1 platform (Quanterix, Lexington, MA) using the Neurology 4-plex A and the Cytokine 3-plex A kits (n=53). Outcome was assessed at 6 months post-injury using the Glasgow Outcome Scale-Extended (GOSE) (n=21). Head computed tomography (CT) scans were classified based on the presence or absence of traumatic intracranial CT abnormalities (n=53). Logistic regression and area under the receiver operator curve (AUC) analyses revealed that the four brain-injury proteins combined (GFAP, UCHL1, NFL, Tau) had excellent discriminative ability for presence/absence of traumatic intracranial abnormality (AUC=0.87.) The brain injury proteins were poorly informative with regards to 6 month full recovery (GOSE=8, AUC=0.66). When all inflammatory biomarkers (IL-6, IL-10, TNF-alpha) were assessed together, they provided prognostic information for 6 month full recovery (GOSE=8, AUC=0.72). The combination of brain-injury proteins and inflammatory cytokines provided excellent prognostic information with regards to 6 month full recovery (GOSE=8, AUC=0.89). These results suggest that the brain injury protein biomarkers have diagnostic potential while the inflammatory biomarkers show potential to add prognostic information for TBI biomarkers. Further study of the longitudinal changes in multiple inflammatory cytokines and their relation to varying clinical outcomes in a larger cohort, may improve prognostic modeling after TBI and impact clinical practice and research.

Disclosures: M. Haber: None. **J. Poddell:** None. **F. Korley:** None. **D. Wilson:** A. Employment/Salary (full or part-time):; Quanterix Corporation. **A.R. Ferguson:** None. **P. Mukherjee:** None. **K. Wang:** None. **A. Valadka:** None. **A. Puccio:** None. **D. Okonkwo:** None. **G. Manley:** None. **R. Diaz-Arrastia:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.06/BB5

Topic: C.10. Brain Injury and Trauma

Title: Sleep-wake disturbances following brain injury and relation to outcome

Authors: *S. N. HOWELL[1], G. S. GRIESBACH[2]
[1]Clin. Res., Ctr. for Neuro Skills, Irving, TX; [2]Clin. Res., Ctr. for Neuro Skills, Encino, CA

Abstract: Objective: To investigate the impact of sleep-wake disturbances (SWD) on cognitive function and quality of life measures following brain injury. Sex differences were investigated. **Methods:** Adult TBI (n=14) and stroke (n=28) patients were assessed for SWD via overnight polysomnography. The mean age was 49.3 ± 2 years and mean latency from injury was 115 ± 15 days. Sleep measures included total sleep time (TST), sleep and REM latency, percent time in sleep stages, apnea/hypopnea index (AHI), wake after sleep onset (WASO), and arousal index. Hormone levels were analyzed within 10 days of PSG. The primary outcome measures were: Montreal Cognitive Assessment (MoCA), Trails, Beck Depression Inventory (BDI-II), Neuro-QoL and Mayo Portland Adaptability Inventory (MPAI).
Results: Analysis of stroke data showed a negative correlation between REM latency and the MPAI ($p<.05$). For female stroke patients, there was a negative correlation between N2 sleep and the MPAI ($p<.01$), while males had significantly higher AHI ($F(1,19)=5.401$, $p<.05$). Percent time spent in REM sleep was positively correlated with IGF-1 levels ($p<.05$). For the TBI population, females spent a higher percentage of time in slow wave sleep (SWS) ($F(1,9)=5.688$, $p<.05$) and less time in REM ($F(1,9)=14.344$, $p<.01$). Females also had significantly higher latencies to REM sleep ($F(1,9)=6.753$, $p<.05$) and scored higher on subjective levels of anxiety, fatigue, and sleep disturbance ($p<.05$). Daytime sleepiness was associated with age ($p<.01$). Age was also positively correlated with the amount of time spent in N2 ($p<.001$) with a corresponding negative correlation with SWS ($p<.05$). Percent time spent in REM was positively correlated with scores on the MoCA ($p<.01$) and Trails ($p<.05$). WASO was also trending towards a negative correlation with MoCA scores ($p=.07$). Overall, 50% of stroke and 38% of TBI patients had sleep apnea. For TBI patients, apnea was not significantly correlated with BMI, which could be indicative of respiratory dysregulation driven by TBI-related autonomic disturbances.
Conclusion: Female patients were more likely to report subjective disturbances in sleep and females with TBI show significant impairments in REM sleep, which is critical for learning and memory. Sleep disturbances were associated with poorer cognitive performance and may ultimately affect outcome.

Disclosures: S.N. Howell: None. **G.S. Griesbach:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.07/BB6

Topic: C.10. Brain Injury and Trauma

Support: Marquette Strategic Innovation Fund (SIF P105)

Title: Does motor memory usage change in concussed individuals performing a sensorimotor adaptation task?

Authors: *D. LANTAGNE[1], L. A. MROTEK[1], S. A. BEARDSLEY[1], D. G. THOMAS[4], D. LEIGH[2], S. I. AHAMED[3], R. A. SCHEIDT[1,5,6]
[1]Biomed. Engin., [2]Exercise Sci., [3]Mathematics Statistics and Computer Sci., Marquette Univ., Milwaukee, WI; [4]Pediatrics, [5]Med. Col. of Wisconsin, Milwaukee, WI; [6]Northwestern Univ., Chicago, IL

Abstract: We examined kinematic errors during practice of goal-directed reaching against unpredictable spring-like loads to quantify the impact of concussion on sensorimotor memories used in implicit learning. Subjects included 20 healthy and 11 concussed college students; each participated in four experimental sessions where they grasped the handle of a horizontal-planar robot while reaching out-and-back to a visual target in the sagittal plane. Sessions: < 100 hours post injury ("Time 0" T_0 for non-concussed individuals); return-to-play (RTP) date (T_0 + 10 days for healthy); +3 and +6 months post injury or T_0. In each session, subjects performed 20 practice reaches with concurrent visual feedback of hand motion. This allowed them to learn the general task requirements. They then performed 200 trials without visual feedback against a spring-like load that changed randomly between trials. This allowed evaluation of the sensorimotor memories used in implicit learning of environmental loads, as well as kinematic performance variables including reach accuracy and target capture time. We assessed concussion symptoms using self-reporting (SCAT-3). We also assessed cognition via CogState Research II computerized testing, which reports performance on executive function, psychomotor function, paired associative learning, attention, visual learning, and declarative working memory. On the first day of testing, we found considerable heterogeneity within the group of concussed individuals; some reported more symptoms than others. In the concussed group for the reaching task, the method by which subjects predicted the next trial's spring load based on the weighted sum of the previous load and reach error changed between the first and second session, but this measure did not change in the Healthy group . This trial-by-trial load prediction reflects a subject's memory integration process as derived from systems identification of memory-based sensorimotor adaptation (Judkins and Scheidt, 2014). We conclude that concussion does indeed

impact how motor memories contribute to the predictive compensation for uncertain environmental loads during sensorimotor adaptation.

Disclosures: D. Lantagne: None. **L.A. Mrotek:** None. **S.A. Beardsley:** None. **D.G. Thomas:** None. **D. Leigh:** None. **S.I. Ahamed:** None. **R.A. Scheidt:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.08/BB7

Topic: C.10. Brain Injury and Trauma

Support: Moody Project for Translational TBI Research

Title: Circulating microRNA expression in acute and chronic human TBI

Authors: *H. A. WEISZ[1], D. BOONE[4], H. SPRATT[2], C. ROBERTSON[5], H. S. LEVIN[6], M. SHEFFIELD-MOORE[3], D. DEWITT[1], D. S. PROUGH[1], H. L. HELLMICH[1]
[1]Anesthesiol., [2]Preventative Med. and Community Hlth., [3]Intrnl. Med., Univ. of Texas Med. Br., Galveston, TX; [4]Anesthesiol., Univ. of Texas Med. Br. At Galveston, Galveston, TX; [5]Neurosurg., Baylor Col. of Med., Houston, TX; [6]Cognitive Neurosci Lab., Baylor Col. Med., Houston, TX

Abstract: There is an unmet need for reliable and minimally invasive biomarkers of traumatic brain injury (TBI). A significant number of brain injury patients cannot be diagnosed with conventional imaging (i.e., CT or MRI). Recent studies suggest that circulating levels of small, non-coding microRNAs (miRNAs), that are post-transcriptional regulators of gene expression, may serve as non-invasive biomarkers of brain injury. Our *objective* in this study was to measure and compare miRNAs in archived serum and cerebrospinal fluid (CSF) samples of human TBI patients with uninjured controls. We *hypothesized* that a specific panel of circulating miRNAs would effectively discriminate TBI patients from uninjured controls. Archived serum (obtained 24, 48, and 96 hours after admission to the emergency department) and CSF samples (24 hours) were acquired from patients with a clinically diagnosed TBI. Serum samples were also obtained from chronic TBI patients (10-15 years after diagnosis). Control serum and CSF samples were prospectively obtained from BioreclamationIVT. RNA was isolated from all serum and CSF samples and enriched for small-RNA species. cDNA libraries were prepared for miRNA sequencing and sequenced on a NextSeq550 Illumina platform. MicroRNA-sequencing data was analyzed using EdgeR. Our *analysis* showed: 1) serum and CSF miRNA levels differentiated TBI from uninjured controls; 2) expression of some miRNAs overlapped in CSF and serum samples; 3) some of the discriminating miRNAs (from 24, 48, and 96 hours) were found persistently dysregulated in chronic TBI patients. Ingenuity Pathway Analysis (IPA) showed that

differentially expressed miRNAs are predicted to regulate genes involved in inflammation and neurodegenerative cell signaling pathways. Bioinformatic analysis suggested that some of these TBI dysregulated miRNAs are linked to deficits in the cognitive domain (i.e., executive function, emotional control, and memory). These miRNA signatures may be useful for prognosis of neuropsychological and psychiatric outcomes in future studies. We *concluded* that circulating miRNA signatures are representative of brain pathology and serum miRNAs may be useful as biomarkers of TBI. Future studies will assess the utility of miRNA signatures for confirmation of TBI subtypes from neuroimaging. MicroRNA profiling may also have therapeutic value for monitoring the recovery of chronic TBI patients.

Disclosures: H.A. Weisz: None. **D. Boone:** None. **H. Spratt:** None. **C. Robertson:** None. **H.S. Levin:** None. **M. Sheffield-Moore:** None. **D. DeWitt:** None. **D.S. Prough:** None. **H.L. Hellmich:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.09/BB8

Topic: C.10. Brain Injury and Trauma

Title: The impact of traumatic brain injury on physiological markers and sleep patterns

Authors: *C. K. SINGH, L. A. KREBER, M. SCHAFER, G. CASTILLO, G. S. GRIESBACH
Ctr. For Neuro Skills, Bakersfield, CA

Abstract: Introduction
Traumatic brain injury (TBI) sequelae may disrupt one's physiological state as well as psychological. Patients may be deconditioned meanwhile their injury negatively impacts their mood resulting in depression, which consequentially affects sleep patterns. Compromised aerobic fitness combined with disturbances in mood and sleep prove to be debilitating sequelae for survivors. The literature reports aerobic exercise positively impacts fitness and mood after TBI. This multipronged study aims to explore the effects of exercise on aerobic fitness while evaluating the impact of mood disturbances on sleep.
Methods
Cardiovascular fitness was assessed via cardio pulmonary exercise testing (CPET) in 12 adults with TBI (M age=32; 92% male; M injury chronicity= 300 days) every 2 weeks until discharge, and baseline comparative testing was performed in 6 healthy, uninjured controls (M age= 31; 83% male). CPET physiological measurements included maximum respiratory oxygen uptake (VO_2 max) and heart rate (HR) during a modification of the Bruce Treadmill Test. Actigraphy was also obtained on these patients. Patients were randomly assigned to a supervised aerobic exercise (E) (three times per week for 30 minutes) or a non-exercise group (NE). Cognitive,

depression, and fatigue measures were administered including Beck Depression Inventory-II (BDI), Epworth Sleepiness Scale, Trail Making Test A and B, and BORG at admission and discharge.
Results
The TBI group had a significantly higher resting HR at baseline than uninjured controls ($p < 0.05$). Furthermore, 33% of the E and 66% of the NE group were below normal VO_2 max norms at baseline. At four weeks, all of E group was above the normal range while 66% of NE group remained below. A significant correlation between BDI and Epworth scores ($r= .843$), as well as, between BDI and Trails A performance existed ($r=.686$; $p <0.05$). Additionally, Epworth scores were positively correlated with BORG scores ($r= .697$; $p <0.05$). Linear regression models revealed the following significant relationships ($p <0.05$): Admission BDI was predictive of time spent in bed and time spent asleep at baseline. Baseline BDI was predictive of wake after sleep onset (WASO) at weeks two, three, and four of the study. Baseline Epworth was predictive of the number of awakenings during week one.
Conclusion
TBI reduces VO_2 max but can be improved through participation in an exercise regimen. Depression after TBI may influence the perception of fatigue, and play a role in irregular sleep patterns. The role of aerobic exercise following TBI and its impact on depression, sleep, and consequently recovery necessitates further investigation.

Disclosures: C.K. Singh: None. **L.A. Kreber:** None. **M. Schafer:** None. **G. Castillo:** None. **G.S. Griesbach:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.10/BB9

Topic: C.10. Brain Injury and Trauma

Support: CCDA

Title: Towards a more ecologically valid and objective measurement of mTBI recovery in adolescents: fNIRs and miRNA reveal underlying physiological differences within an expected window of recovery

Authors: N. SIDEMAN[1], H. AYAZ[2], C. J. HAMMOND[3], A. SARGENT[2], D. M. APPELT[6], S. L. ALLEN[4], *B. J. BALIN[5]
[1]Neurol., Thomas Jefferson Univ. Hosp., Philadelphia, PA; [2]Sch. of Biomed. Engin., Drexel Univ., Philadelphia, PA; [3]Div. of Res., [4]Psychology, [5]Bio-Medical Sci., Philadelphia Col. of Osteo. Med., Philadelphia, PA; [6]Ctr. for Chronic Disorders of Aging, Philadelphia Col. Osteo. Med., Philadelphia, PA

Abstract: OBJECTIVES: The majority of individuals with mTBI return to baseline after injury at 2-4 weeks. Our previous work has shown resolution of neurocognitive deficits and emotional dysfunction associated with mTBI. Controversy exists about the subjectivity of self-report measures and the lack of sensitivity in neurocognitive measures raising the question if "full recovery" actually does occur within this time frame. Therefore, we used functional near infrared spectroscopy (fNIRS) and miRNA analyses on subjects with and without a recent mTBI to see recovery via objective measures of biological functioning. We also explored the potential modulating influence that emotions, symptom severity, days post injury, etc. have on these biological measures of functioning. METHODS: Adolescent athletes (n=13), nearly all within 4 weeks of injury, were compared to age matched non-injured athletes (n=12). Subjects (14 F, 11 M, ages 14-17) completed behavioral tasks (N-back and math fluency). miRNA, known to influence gene expression, was analyzed from subjects' saliva. Post-concussion symptom, smell identification, and emotional rating scales were also completed. RESULTS: Subjects did not differ in age, gender, education, handedness, or hours of sleep. Average age was 16 years (SD+/-1.26) and mean time since injury was 19.5 days (SD+/-7.7). Minimal differences in behavioral performance, smell identification, and emotional ratings were found between groups. Medial/lateral optode grouping were significantly greater for the mTBI group (p= .006) during the math fluency task. These findings remained stable even when anxiety, gender, previous concussion history, age, and grade were used as covariates. The difference between medial/lateral optode grouping activations was significantly greater in the high depressive symptom (p &lt.001) and high anxious symptom groups (p&lt.001). Female participants with mTBI displayed lower activation overall, but displayed higher left lateral optode activation during the math task (p = .031). miRNA analyses revealed significant differences between experimental groups and between specific mTBI subgroupings. CONCLUSIONS: Our findings captured through non-invasive measures revealed significant differences between groups and within mTBI subgroupings. This suggests that a more objective assessment of mTBI may provide a more comprehensive view of recovery. fNIRS and miRNA analyses should be considered when standard measures lack sensitivity. An interrelationship between emotional, behavioral and biological functioning was also found, suggesting the need for a more holistic evaluation of adolescents with mTBI.

Disclosures: N. Sideman: None. **H. Ayaz:** None. **C.J. Hammond:** None. **A. Sargent:** None. **D.M. Appelt:** None. **S.L. Allen:** None. **B.J. Balin:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.11/BB10

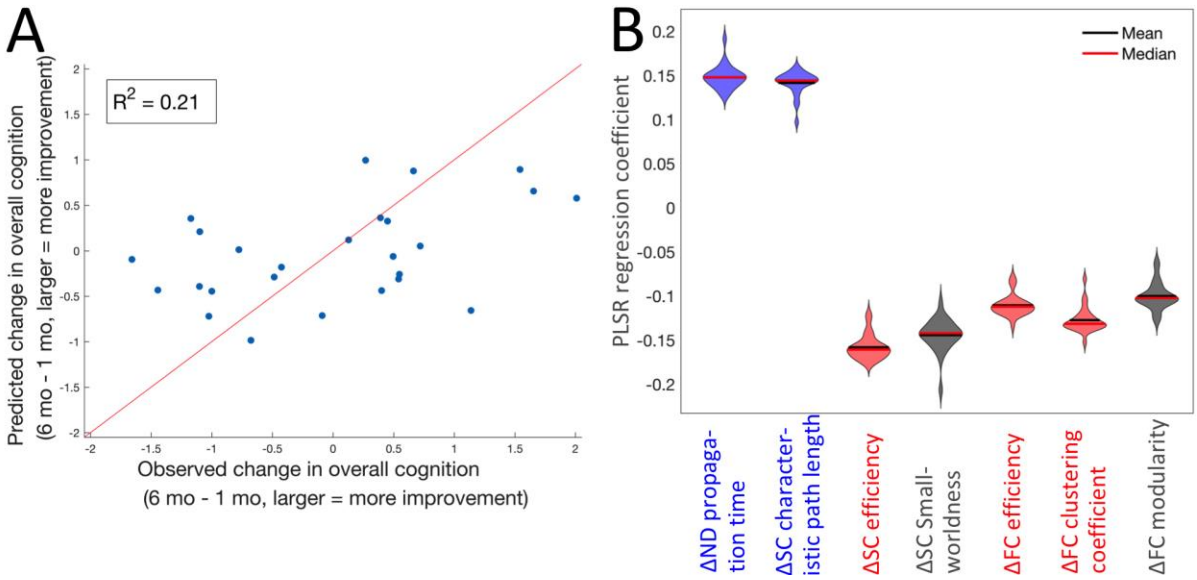
Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R01 NS060776
NIH Grant R01 NS102646
NIH Grant R21 NS104634
Anna-Maria and Stephen Kellen Foundation

Title: Functional rerouting along the structural connectome is associated with improved cognitive recovery after mild traumatic brain injury

Authors: *P. MUKHERJEE[1], K. W. JAMISON[2], J. P. OWEN[3], A. RAJ[4], A. KUCEYESKI[2]
[1]Professor of Radiology & Bioengineering, Univ. of California San Francisco, San Francisco, CA; [2]Weill Cornell Med. Col., New York, NY; [3]Radiology, Univ. of Washington, Seattle, WA; [4]Radiology and Biomed. Imaging, Univ. of California, San Francisco, San Francisco, CA

Abstract: Traumatic brain injury damages white matter pathways that connect brain regions, disrupting transmission of electrical signals and causing cognitive and emotional dysfunction. Recovery occurs over weeks or months in some, while others suffer chronic and debilitating impairment. The mechanism for how the brain compensates for injury has not been fully characterized. Here, we collect global structural and functional connectome metrics (derived from diffusion and resting-state functional MRI, respectively) and neuropsychological scores in 26 mild traumatic brain injury subjects (29.4±8.0 years, 20 male) at 1 month and 6 months post-injury. We quantified the relationship between functional and structural connectomes using network diffusion model propagation time, a measure of how much of the structural connectome is being used for the spread of functional activation. None of the structural or functional connectome metrics were significantly different between one and 6 months, or when either time point was compared to a group of 34 age- and gender-matched controls (28.6±8.8 years, 25 male). We predicted longitudinal changes in overall cognitive function from changes in connectome measures using a partial least squares regression model with leave-one-out cross validation ($R^2 = 0.21$, Fig 1A). Longitudinal increases in network diffusion model propagation time and structural connectome characteristic path length, along with decreased structural and functional connectome efficiency and functional connectome clustering coefficient were significant predictors of better improvements in overall cognitive function (Fig 1B). These findings align with our previous cross-sectional work showing increased network diffusion model propagation time was correlated with recovery after severe brain injury. We interpret our findings as support for the "functional rerouting" hypothesis, wherein irrevocably damaged structural connections are compensated for by rerouting of functional connections along alternate, possibly less efficient, structural connectivity pathways.



Disclosures: **P. Mukherjee:** 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.; GE Healthcare. Other; GE-NFL Medical Advisory Board. **K.W. Jamison:** None. **J.P. Owen:** None. **A. Raj:** None. **A. Kuceyeski:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.12/BB11

Topic: C.10. Brain Injury and Trauma

Support: CIHR MOP 125915

Title: Sex-related differences in the effect of concussion history on cognitive-motor integration performance in varsity athletes

Authors: ***A. PIERIAS**[1], D. J. GORBET[2], T. MELOCHE[3], L. M. HYNES[4], M. WOJTOWICZ[5], L. E. SERGIO[4]
[2]Ctr. for Vision Res., [1]York Univ., North York, ON, Canada; [3]Sport Med., [4]Sch. of Kinesiology and Hlth. Sci., [5]York Univ., Toronto, ON, Canada

Abstract: Cognitive-motor integration (CMI) is required when a rule is used to align the required motor output to spatially dissociated visual information, a situation prevalent in many sports. Previous cross-sectional research from our laboratory[1,2] has shown CMI deficits in

university-level, child, and adolescent athletes with a history of concussion (but were deemed recovered and symptom-free at the time of evaluation). Multiple concussion history may negatively impact executive function abilities[3], reaction time[4], and time to recovery[4]. As well, it has been shown that there are sex differences both in functional brain activity underlying CMI performance, and in the effects of concussion. Therefore, in the current study, we examine the interaction between sex, concussion history, and CMI performance. Participants included 14 male and 14 female varsity athletes with a history of one or more concussions. Participants were tested on two visuomotor transformation tasks. In both conditions, participants viewed targets for visually-guided reaching movements on a vertical touch screen and moved a cursor from a central target to one of four peripheral targets (up, down, left, right) by sliding their finger. Condition one was a "standard" visuomotor mapping task where participants hand movements were made on the vertical touch screen (i.e. gaze and hand responses were spatially congruent). In condition two, participants looked at targets on the vertical screen but made their hand movements on a horizontal touchpad, with the cursor feedback 180^{o} reversed so that the motion plane and cursor alignment were decoupled from guiding visual information (i.e. a non-standard visuomotor mapping requiring CMI). Overall, men and women did not significantly differ in performance on the tasks. In contrast, we observed significant differences between the effects of number of concussions on males versus females. In males, number of concussions had a strong negative correlation ($p<0.05$) with reaction time, a strong positive correlation with peak velocity ($P<0.05$), which was not seen in females. As well, we see a strong positive correlation with number of unsuccessful trials only in males with a history of more than one concussion. These results suggest that males and females respond differently to repeated injury and therefore may require different tools for clinical diagnoses, outcome projections, and recovery assessment. References: 1.Brown et al.2015, BMC Sports Sci Med Rehabil.7(1):25;2. Dalecki et al.2016. Concussion, Vol. 1(3);3. Belanger et al. 2010, J Int Neuropsych Soc.16(2):262-7;4. Covassin et al.2013, Am J Sports Med. 2013 Dec;41(12):2885-9.

Disclosures: A. Pierias: None. **D.J. Gorbet:** None. **T. Meloche:** None. **L.M. Hynes:** None. **M. Wojtowicz:** None. **L.E. Sergio:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.13/BB12

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant K23HD06161
NIH Grant UL1TR001079-04

Title: Subtle motor signs and executive function in chronic pediatric traumatic brain injury

Authors: *J. CRASTA[1], B. S. SLOMINE[4], S. MOSTOFSKY[2], S. SUSKAUER[3]
[2]Dept. of Neurol., [3]Physical Med. and Rehabil., [1]Johns Hopkins Univ., Baltimore, MD; [4]Kennedy Krieger Inst., Baltimore, MD

Abstract: The chronic effects of pediatric traumatic brain injury (TBI) on cognition and behavior even in children with overall good recovery are well established. In other developmental disorders, subtle motor deficits have been shown to be related to executive functioning. Chronic subtle motor deficits have not been examined in pediatric TBI. This study examined the relationship between subtle motor deficits as measured by a "bedside exam", and executive functioning measured using a performance-based Go/No-Go task and a parent-report questionnaire and examined the neural correlates of subtle motor deficits in children with TBI. Sixteen children with moderate or severe TBI, ages 11-18 years, who had sustained their injury at least 1 year prior to study participation (Range 1-14 years since injury), and 16 age-matched typically developing controls were examined using the Physical and Neurological Examination of Subtle Signs (PANESS) and a simple (minimized cognitive demands) Go/No-Go task. Parents completed the Behavioral Rating Inventory of Executive Function (BRIEF). Measures of total cerebral volume (TCV) and motor/premotor volume were derived from MRI. The TBI group showed significantly more subtle motor deficits, including more proximal and mirror overflow movements on the PANESS, and significantly more executive functioning deficits on the BRIEF, compared to controls. On the Go/No-Go task, the TBI group showed significantly more commission errors and higher intrasubject variability (ISV) in response times than controls. Across all participants, greater proximal overflow correlated with greater deficits on the BRIEF (r = .4, p = .03) and increased ISV (r = .43, p = .01). Across all participants, MRI analyses revealed significant correlations between PANESS total score and motor/premotor volume (r = -.5, p = .005), and between proximal overflow and TCV (r = -.41, p = .027), such that lower volume correlated with greater subtle motor deficits. The study highlights the importance of examining subtle motor signs including overflow during clinical evaluation of chronic pediatric TBI and establishes the clinical utility of the PANESS as a measure sensitive to chronic subtle motor signs in this population. The correlation between persistence of overflow and real-world behavior suggests that overflow may be a marker of broader dysfunction in TBI. Further research is required to examine the neural basis of overflow and the relationship between overflow and cognitive performance in pediatric TBI.

Disclosures: J. Crasta: None. **B.S. Slomine:** None. **S. Mostofsky:** None. **S. Suskauer:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.14/BB13

Topic: C.10. Brain Injury and Trauma

Support: Dana Foundation
Tiny Blue Dot Foundation

Title: Low intensity focused ultrasound in disorders of consciousness: A preliminary report

Authors: *M. M. MONTI[1], C. SCHNAKERS[5], J. A. CAIN[1], J. P. COETZEE[2], N. M. SPIVAK[3], P. M. VESPA[4]
[2]Psychology, [3]Dept. of Psychiatry and Biobehavioral Sci., [4]Neurol., [1]UCLA, Los Angeles, CA; [5]Res. Inst., Casa Colina Rehabil. Hosp., Pomona, CA

Abstract: Despite a growing understanding of brain mechanisms underlying loss and recovery of consciousness in the clinical setting, there is still little that can be done for helping patients recover consciousness after severe brain injury (Schnakers & Monti, 2017). To date, the only intervention that has been shown to be effective relies on pharmacological modulation of the thalamo-cortical system (e.g., with amantadine). Other neuromodulatory approaches, based on neurostimulation, such as DBS and tDCS have also been attempted. Here we present a novel approach, based on Low Intensity Focused Ultrasound Pulsation (LIFUP), aimed at upregulating the thalamo-cortical system by directly stimulating thalamus with a non-invasive technique. Specifically, we recruited a convenience sample of acute (< 1 month; N=7) and chronic (> 1 year; N=2) patients with disorders of consciousness for an exploratory clinical trial. The protocol included 2 LIFUP sessions -- one week apart -- preceded and followed by behavioral assessment (with the Coma Recovery Scale - Revised; Giacino et al, 2004) and by neuroimaging testing. In our initial sample, LIFUP shows positive correlation with behavioral recovery, in both acute and chronic patients. From a safety standpoint, all of our patients either ameliorated after the procedure (whether serendipitously or because of our stimulation) or simply showed no change, confirming the excellent safety record of ultrasound and focused ultrasound. These preliminary results suggest that LIFUP might be a potential novel technique to help patients recover consciousness after severe brain injury which combines the non-invasiveness of TBS with the ability of DBS to directly modulate deep nuclei of the brain.
Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. *Archives of physical medicine and rehabilitation*, *85*(12), 2020-2029.
Schnakers, C., & Monti, M. M. (2017). Disorders of consciousness after severe brain injury: therapeutic options. *Current opinion in neurology*, *30*(6), 573-579..

Disclosures: C. Schnakers: None. **J.A. Cain:** None. **J.P. Coetzee:** None. **N.M. Spivak:** None. **P.M. Vespa:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.15/BB14

Topic: C.10. Brain Injury and Trauma

Support: BGSU Research Incentive Grant

Title: Differential patterns of neural activation related to emotional face recognition in short-term and long-term recovery from concussion:Two fMRI case studies

Authors: J. RICKER[1], K. A. SMITH[1], A. SCHMIDT[2], A. E. CRIPPS[2], P. THALLA[3], *H. C. CROMWELL[2], X. WANG[4]
[1]Psychology, [2]Bowling Green State Univ., Bowling Green, OH; [4]Psychiatry, [3]Univ. of Toledo, Toledo, OH

Abstract: Concussions are heterogeneous injuries that occur at high rates in the United States. It is estimated that anywhere from 300,000 to 3.8 million concussions occur in any given year. Given this prevalence, there is a dire need to understand the neurological effects of this injury, as well as how the brain may recover. While there is a wide range of symptoms that can follow sustaining a concussion, the effects on all aspects of emotion have rarely been studied. One way in which concussions may affect cognition is through the ability to properly assess emotions being displayed by conspecifics. With each concussion being vastly different, group analyses may not detect differences in those with concussions due to large group variability. The current study sought out to understand the behavioral and neural effects that a history of concussion may have while taking the approach similar to that used in precision medicine. Five healthy control subjects performed an emotional face assessment task (EFAT) while in an fMRI scanner, and results were compared to two collegiate hockey players with a history of concussion. One player had sustained his most recent concussion approximately one year prior to testing (long-term recovery), while the other had sustained his most recent concussion 16 days prior to testing (short-term recovery). Control subjects showed neural activation profiles similar to that which was expected from previous research on emotional assessment. The long-term recovery case displayed a profile that differed from the control subjects with activation in areas outside of those expected. The short-term recovery case displayed no significant activation in any regions while performing the EFAT. These results demonstrate that the length of time since sustaining a concussion may determine how neural activation varies in cognitive tasks.

Disclosures: J. Ricker: None. **K.A. Smith:** None. **A. Schmidt:** None. **A.E. Cripps:** None. **P. Thalla:** None. **H.C. Cromwell:** None. **X. Wang:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.16/BB15

Topic: C.10. Brain Injury and Trauma

Title: Time-dependent prefrontal white matter differences and changes in attentional bias to threat following mild traumatic brain injury

Authors: *J. M. CARLSON[1], T. SUSA[2], M. T. MOORE[3]
[1]Psychology, [2]Psychology/Neuroscience, [3]Sch. of Hlth. and Human Performance, Northern Michigan Univ., Marquette, MI

Abstract: Magnetic resonance imaging (MRI) has been used to assess disturbances in brain function and structure following mild traumatic brain injury (mTBI). As of yet, however, there is no definitive MRI-based biomarker of mTBI or its associated symptoms. Recently, it has become clear that time since injury is critically related to changes in brain structure following mTBI. Although the prefrontal cortex (PFC) is typically affected by mTBI and plays an important role in affective processing, little is known about the time-dependent relationship between PFC disturbances and affective symptoms accompanying mTBI. This study aimed to better understand this relationship by collecting MRIs from a sample of 30 collegiate student athletes. Half of the participants (n = 15) were recently cleared to return to play after experiencing a sports-related concussion. The other half of participants (n = 15), had not experienced a concussion within the past year and were matched on age, sex, and sport. A dot-probe task with fearful and neutral faces was used to assess participants' attentional bias to threat by comparing reaction times to targets at locations previously occupied by fearful vs. neutral faces. To assess participants' more general affective symptoms, the depression, anxiety, and stress scale (DASS) was administered. Levels of depression, anxiety, and stress were all elevated in the mTBI group. Bilateral differences in PFC white matter were observed between groups. This affect was time-dependent such that white matter increased as time since injury increased. Time since injury also correlated with attentional bias such that attentional bias increased as the time since injury increased. PFC white matter and attentional bias to threat were positively correlated. The results add to a growing body of work indicating that time since injury is an important consideration when looking at structural changes following mTBI and that white matter increases post-mTBI are accompanied by an increase in attentional bias to threat.

Disclosures: J.M. Carlson: None. **T. Susa:** None. **M.T. Moore:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.17/BB16

Topic: C.10. Brain Injury and Trauma

Support: USUHS HU0001-15-2-0024

Title: Associations between chronic low-level blast exposure and combat experience with personality, mood, and cognition

Authors: A. A. QUICK[1,3,4], M. TIERNEY[3], E. M. WASSERMANN[3], S. T. AHLERS[2], E. POLEJAEVA[3,5,6], K. DELL[7,9,3], W. CARR[6], M. L. LOPRESTI[8], C. GOFORTH[2,10,1], *C. M. MODICA[1]
[1]Neurotrauma, [2]Operational and Undersea Med., Naval Med. Res. Ctr., Silver Spring, MD; [3]Natl. Inst. of Neurolog. and Disorders and Stroke, Bethesda, MD; [4]Henry M. Jackson Fndn. for the Advancement of Military Med., Bethesda, MD; [5]Univ. of Florida, Gainesville, FL; [7]Behavioral Biol. Br., [8]Psychiatry and Neurosci., [6]Walter Reed Army Inst. of Res., Silver Spring, MD; [9]Pennsylvania State Univ., University Park, PA; [10]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: There is question of whether chronic, low-level blast exposure impacts neurological/cognitive function. This study aimed to characterize symptoms and neuropsychological (NP) profiles of 20 experienced explosives specialists (career breachers) compared to 14 military/law enforcement personnel who were not breachers. Demographics, 46 self-report symptoms/responses, combat exposure checklist (CEC), 23 NP scores, and companion questionnaires were compared, with added analysis in subgroups of military only and those with lower combat experience. Due to the large volume and array of tests conducted, significance was set at $p<0.01$ to avoid Type I error, yet symptoms, NP tests, and companion test scores meeting $0.01<p<0.05$ were still carried forward alongside differing variables in hierarchical logistic or linear regressions with breaching experience. Breachers were exposed to more combat experiences than non-breachers, even in the low combat subgroup (CEC $p<0.01$, ANOVA). Military subgroup breachers reported more ringing in ears ($p<0.01$, Pearson Chi-square). Self-reported symptoms at $0.01<p<0.05$ in all breachers included memory and concentration problems, ringing in ears, and irritability, with light/noise sensitivity only in the low combat breachers (Pearson Chi-square). However, reported memory and concentration problems were also associated with CEC. Since CEC predicted outcomes more often than breaching experience, further tests controlled for CEC. Breachers performed better than non-breachers on subsets of the CVLT ($p<0.01$, ANOVA) and were slightly elevated on subtests of WASI and ImPACT ($0.01<p<0.05$, ANOVA). Slightly higher PTSD and lower vigor scales in

breachers ($0.01<p<0.05$ PCL-M and ANAM vigor; Mann Whitney U) disappeared after controlling for CEC, as did the ImPACT subtest. Low-combat breachers exhibited slower reaction times only after controlling for CEC (ANAM SRT: $p<0.01$, $0.01<p<0.05$ for ImPACT reaction time; ANCOVA). Breaching experience improved the model predicting NEOFFI conscientiousness in addition to CEC (F change $p<0.01$). In conclusion, breachers (specifically military) were associated with ringing in ears and better performance on a verbal learning task (CVLT). There may be baseline differences in learning and memory in those chosen for careers in explosives. When controlling for combat experience, a pattern of slower reaction time arose in breachers, and breaching experience predicted a better conscientiousness score. Combat exposure was a distinct contributor to outcomes, and should be explored further. Future analysis should focus on mediators of differential outcomes in blast-exposed personnel.

Disclosures: A.A. Quick: None. **M. Tierney:** None. **E.M. Wassermann:** None. **S.T. Ahlers:** None. **E. Polejaeva:** None. **K. Dell:** None. **W. Carr:** None. **M.L. LoPresti:** None. **C. Goforth:** None. **C.M. Modica:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.18/BB17

Topic: C.10. Brain Injury and Trauma

Title: A review of tools used to prevent or diagnosis concussions in sports

Authors: *A. ADAMI[1,2], J. VILLAPANDO[2]
[1]Res., San Diego Miramar Col., San Diego, CA; [2]Alpha Fiber, San Diego, CA

Abstract: Background: Mild traumatic brain injury (TBI) is a major public health concern as subsequent injuries in quick succession can intensify existing neuropathology making the brain vulnerable to acute and long-term neurological deficits. With over 2 million incidences of sports-related concussions (SRC) annually in the US, there is a critical need for objective assessment of forces sustained by the head. As technological advances continue to improve our understanding of SRC, little data has been available to the public correlating head impact and neurological deficits. The aim of this review was to investigate the validity of available tools to prevent or diagnosis concussions during athletic competitions. **Methods:** Primary research data were gathered using PubMed, Google Scholar, uspto.gov, clinicaltrials.gov, and a general google search. Published marketing materials were gathered using company websites, published interviews, and social media platforms. Our search yielded 16 commercially available tools and devices related to SRC. Devices were divided into 3 categories based on their primary use: (1) protective equipment used to reduce concussive injuries (2) recording devices to track head movement during impact, and (3) clinical evaluation used post-impact to confirm diagnosis.

Results: Biomechanical data were not available for 12 out of the 16 tools, and limit data were found for the other devices. No data were published from controlled trials in the US related to SRC devices. Without clinical data, marketing material for these devices suggested the ability to reduce the incidence of concussions. Angular and linear acceleration data published from wearable devices have primarily come from laboratory simulations. **Conclusion:** Little is known regarding the correlation of the type of impact sustained by the brain and acute/chronic neurological deficits. Recently, devices have been developed to diminish the impact to the brain or objectively monitor the force of the impact. Despite positive reviews for each device, there have only been a limited number of peer-reviewed publications and no independent laboratory evaluations of these devices. Increased transparency with collected data can exponentially improve our understanding of the cause of concussions.

Disclosures: A. Adami: None. **J. Villapando:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.19/CC1

Topic: C.10. Brain Injury and Trauma

Support: NIH R21-5R21DC013974
Indiana Spinal Cord and Brain Injury Research Fund
NSF IIS-1636893
NSF BCS-1734853
Microsoft Research
Indiana University Areas of Emergent Research Initiative “Learning: Brains, Machines, Children”
Indiana Pervasive Institute

Title: Advanced white matter mapping in the subconcussive brain

Authors: *B. A. CARON, F. PESTILLI, N. PORT
Indiana Univ., Bloomington, IN

Abstract: Background: The topic of behavioral and structural deficits caused by concussions is an increasingly important one in the related research fields. With an incidence rate of 2.9 competition concussions per 1,000athlete exposures (NCAA 2013)in collegiate football, the concussion risk to athletes is significant. However, even subconcussive blows, or blows that do not lead to a concussion diagnosis, appear to create health risks for athletes. These impacts appear to lead to significant neural changes, the severity of which may depend on the number of hits (McAllister et al, 2014).

ObjectivesandMethods: An anatomically informed, personalized-medicine tractography approach was used to determine which major white matter tracts showed the greatest degree of difference in white matter tensor measures between 17Division I upperclassmen football players, 15Division I upperclassman cross-country runners, and 9 socioeconomically-matched non-athlete controls. We determined the underlying microstructural white matter biomarkers, using a classic diffusion-tensor model (Pierpaoli and Basser, 1999)as well as Neurite Orientation Dispersion and Density Imaging (NODDI; Zhang et al, 2012), that predict differences across different white matter tracts in the groups of athletes.
Results: Results show widespread differences in white matter tissue properties in multiple tracts and among the three athletes groups, including decreased FA, increased ICVF, and OD in the football players versus the two control groups. These differences occurred more often in longer fiber tracts compared to shorter fiber tracts, suggesting a differential effect of head impacts based on the geometric properties of these tracts. As result of this work we also advanced methods for open neuroscience for the Big Ten and Concussion community. We developed a fully automated processing pipeline for this study. The pipeline is made available both as open source code as well as open service at www.brainlife.io . The open service will allow other investigators in the community to process new data using cloud computing and reuse the advanced mapping methods developed in this work.
Conclusions: These results support the hypothesis that multiple subconcussive blows can result in white matter structural changes, with differential effects based on the length of the fiber tract being investigated, that are detectable with diffusion MRI and tractography.

Disclosures: B.A. Caron: None. **F. Pestilli:** None. **N. Port:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.20/CC2

Topic: C.10. Brain Injury and Trauma

Support: NIH National Institute of Neurological Disorders and Stroke Grant U54NS100064

Title: The role of paravascular spaces for epileptogenesis after traumatic brain injury

Authors: *G. BARISANO[1,2], D. DUNCAN[1], F. SEPEHRBAND[1], R. CABEEN[1], H. KIM[1], P. VESPA[3], A. W. TOGA[1], M. LAW[1,2]
[1]USC Stevens Neuroimaging and Informatics Inst., USC, Los Angeles, CA; [2]Dept. of Radiology, Keck Med. Ctr. of USC, Los Angeles, CA; [3]Neurol., UCLA, Los Angeles, CA

Abstract: Objective: The occurrence of seizures after head trauma is a recognized cause of disability in traumatic brain injury (TBI) patients. Post-traumatic epilepsy (PTE) accounts for 10-

20% of symptomatic epilepsy in the general population. Despite the efforts made by the scientific community, the pathophysiologic mechanisms of PTE are not fully understood. Moreover, the identification of reliable biomarkers to predict and diagnose PTE may be particularly helpful for future clinical trials. Many studies have shown that Paravascular Spaces (PVSs) may play an important role in neuroinflammation: a strong post-traumatic inflammatory reaction was documented in PVSs of contused human brain tissue, suggesting that PVSs' impairment could explain the altered macrophage activity resulting in seizure onset. Also, structural changes in PVSs may affect their surrounding white matter networks. We investigate the role of PVSs in TBI as a potential biomarker for PTE.
Methods: We analyzed clinical and MRI data in 15 patients (age range: 7-68 years old) who suffered a moderate-severe TBI using data collected in the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx). MRI scans were performed 14 days after trauma using 3T MRI. 6 healthy subjects (age range: 12-62 years old) were used as controls. PVSs were analyzed on 3D T2-TSE sequences and were defined as tubular-linear or round-ovoid hyperintense structures with a diameter < 3 mm. Diffusion tensor imaging (DTI) technique was used to measure the diffusivity of water molecules in the specific regions where PVSs were identified.
Results: In TBI patients, we found a highly asymmetric PVSs distribution in the two cerebral hemispheres compared with controls. Patients who experienced at least 1 seizure within 6 months after the trauma presented the most asymmetric PVSs distribution. Lateralized Periodic Discharges were detected on EEG, and in all cases the affected hemisphere matched with the hemisphere where less PVSs were identified. Moreover, PVSs mean caliber in the affected hemisphere was smaller compared with the contralateral side. Changes in diffusion metrics were detected as well.
Conclusions: The occurrence of PTE is a clinically relevant complication of TBI. The evaluation of PVSs distribution and quantification may represent a potential noninvasive neuroimaging biomarker to predict the development of epilepsy after TBI. Moreover, PVSs structural analysis combined with DTI analysis can be helpful to define the suspected seizure onset area. Ultimately, these results may be of benefit for the design of future clinical trials and for the evaluation of new possible therapeutic targets.

Disclosures: G. Barisano: None. **D. Duncan:** None. **F. Sepehrband:** None. **R. Cabeen:** None. **H. Kim:** None. **P. Vespa:** None. **A.W. Toga:** None. **M. Law:** None.

Poster

664. Brain Injury and Trauma: Human Studies I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 664.21/CC3

Topic: C.10. Brain Injury and Trauma

Title: Highly sensitive single molecular array immunoassay measurement of t-Tau, NF-L, GFAP, and UCH-L1 biomarkers in concussion/mild traumatic brain injury serum samples

Authors: A. CHENNA[1], C. J. PETROPOULOS[2], *J. W. WINSLOW[3]
[1]Monogram Biosci. Inc, Lab. Corp. of America, Inc, South San Francisco, CA; [2]Monogram Biosciences, Lab. Corp. of America, Inc., South San Francisco, CA; [3]Oncology R&D, Monogram Bioscience/Labcorp Specialty Testing, South San Francisco, CA

Abstract: Central nervous system (CNS) proteins released into cerebral spinal fluid (CSF) and peripheral blood have been associated with brain injury, and are candidate prognostic biomarkers of concussion and mild to moderate traumatic brain injury (mTBI). The accurate and reproducible measurement of these markers in blood requires highly sensitive detection technologies. Recently, single molecular array immunoassays have enabled the accurate quantitation of candidate concussion/mTBI protein biomarkers in blood. In this study, to more fully assess assay analytical performance and characterize CNS protein markers of mTBI in human serum, single molecular array 2-site immunoassays utilizing microfluidic and paramagnetic bead digital technology (Quanterix Simoa) were performed in a multiplex format to generate quantitative measurements of total Tau (t-Tau), neurofilament light chain (NF-L), glial fibrillary acid protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1). Two sample groups consisting of 30 concussion/mTBI patients each, with blood collected within 1-4 hr (avg =1.8 hr) and 8-16 hr (avg = 12.5 hr) post-injury, respectively, were compared with healthy controls. A significant elevation of median GFAP levels was observed in both the 1-4 hr ($p = 0.013$) and 8-16 hr ($p = 0.029$) concussion/mTBI groups relative to controls. A similar increase in median UCH-L1 trended toward significance for both groups. These observations are consistent with previous reports describing both proteins as acute biomarkers of TBI (Papa et al., *JAMA Neurol*. 2016; 73 (5):551-560). With the exception of t-Tau, the median levels of the other three biomarkers trended toward higher levels in the 1-4 hr post-injury sample group relative the 8-16 hr group. Several individuals displayed elevated levels of biomarker combinations providing further support for the utility of ultra-sensitive multiplex CNS protein measurements in serum. Correlations between the serum protein levels overall were observed between t-Tau and UCH-L1, and NF-L and GFAP in the 1-4 hr post-injury sample group ($r = 0.56$-0.65; $p < 0.001$). These two correlations were also significant in the 8-16 hr sample group, including a correlation between NF-L and UCH-L1 ($r = 0.45$-0.65; $p < 0.01$). These correlations suggest that increases in serum t-Tau and NF-L may be observed in larger datasets or with extended post-injury time points. This study supports the multiplex immunoassay capability to detect increases in CNS proteins at high sensitivity in serum within 1-4 and 8-16 hr of concussion/mTBI.

Disclosures: A. Chenna: A. Employment/Salary (full or part-time):; Monogram Biosciences. **C.J. Petropoulos:** A. Employment/Salary (full or part-time):; Monogram Biosciences/Laboratory Corporation of America. **J.W. Winslow:** A. Employment/Salary (full or part-time):; Monogram Bioscience.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.01/CC4

Topic: C.10. Brain Injury and Trauma

Support: CIHR CGS-M

Title: Conditioning electrical stimulation to enhance motor and sensory recovery following peripheral nerve injury

Authors: *J.-L. SENGER[1], M. CHAN[2], H. MACANDILI[1], V. M. K. VERGE[4], K. E. JONES[3], C. CHAN[1], C. A. WEBBER[1]
[1]Dept. of Surgery, [2]Dept. of Physical Med. & Rehabil., [3]Dept. of Biomed. Engin., Univ. of Alberta, Edmonton, AB, Canada; [4]Dept. of Anat. and Cell Biol., Univ. of Saskatchewan, Saskatoon, SK, Canada

Abstract: Background: Peripheral nerve regeneration is often incomplete with significant personal and socioeconomic costs. Although it is known that conditioning lesion (a nerve crush delivered prior to injury and repair) markedly accelerates nerve regrowth, clinical translation is impossible because it is unethical to intentionally injure a healthy nerve. In a proof of principle study, we showed that conditioning electrical stimulation (CES) of the fibular nerve enhances upregulation of regeneration-associated-genes (RAGs) and axonal growth. Whether similar beneficial effects can be generalized to other nerves and whether CES improves functional recovery remain unknown. This knowledge is critical before applying CES for clinical use. **Objectives:**To determine if CES upregulates RAGs, enhances nerve regeneration and improve sensorimotor function in a rat tibial nerve injury model.**Methods:** Sprague Dawley rats were divided based on the type of conditioning to the tibial nerve: i) CES, ii) conditioning crush lesion (CCL), iii) sham-CES controls, and iv) unconditioned controls. Expression of RAGs (GAP43, BDNF, pCREB, GFAP) were analyzed at 3-days post-conditioning (n=3). The length of regeneration was assessed at 7-days (n=6), and physiological and behavioral testing was performed at 7-weeks post-coaptation (n=10).**Results:**There was significantly increased axonal growth in animals conditioned with CES (6.35 ± 1.0 mm) and CCL (6.73 ± 1.0 mm) compared to controls (sham-CES, 2.67 ±0.5 mm; unconditioned, 2.78 ± 0.9 mm). There was a similar pattern of upregulation of RAG expression comparing CES and CCL to controls ($p<0.001$-$p<0.001$). Sensory testing (von Frey filaments, intraepidermal nerve fiber density counts), gait analysis (toe spread evaluation, horizontal ladder testing) and gastrocnemius muscle reinnervation (muscle weight, neuromuscular junction analysis) were significantly improved in the CES animals compared to not only the controls ($p<0.001$-$p<0.001$), but also the crush-conditioned cohort ($p<0.5$). Nerve conduction studies showed significantly larger compound muscle action potential

amplitude in CES compared to controls ($p<0.01$).**Conclusions:**Our data suggests preoperative electrical stimulation delivers a conditioning-like effect in the tibial nerve, with upregulation of RAGs and enhanced axonal outgrowth. Interestingly, CES induced improvements in sensorimotor outcomes beyond those obtained with traditional methods of conditioning. As electrical stimulation is safe and well-tolerated by patients, CES is a clinically feasible intervention that may improve the sensorimotor recovery of patients with peripheral nerve injury.

Disclosures: J. Senger: None. **M. Chan:** None. **H. Macandili:** None. **V.M.K. Verge:** None. **K.E. Jones:** None. **C. Chan:** None. **C.A. Webber:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.02/CC5

Topic: C.10. Brain Injury and Trauma

Support: University Hospital Foundation
Edmonton Civic Employees Charitable Fund

Title: Conditioning electrical stimulation before peripheral nerve repair surgery promotes greater motor and sensory nerve regeneration than postoperative electrical stimulation

Authors: *C. A. WEBBER[1], J.-L. SENGER[2], H. MACANDILI[2], A. CHAN[2], K. CHAN[3]
[1]Div. of Anat., [2]Dept. of Surgery, [3]Dept. of Physical Rehabil., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Background: The use of brief postoperative electrical stimulation (ES) to enhance peripheral nerve regeneration is well described in the literature, and is the current standard of care at many centers. This treatment enhances staggered regeneration at the site of coaptation, with no effect on more distal regrowth. By contrast, a conditioning lesion, the intentional crush to a nerve prior to its cut and repair, accelerates regeneration along the entire length of the distal stump. We have recently shown that preoperative electrical stimulation delivers a conditioning-like effect (conditioning ES, CES). To establish the optimal treatment strategy, we compared the regeneration and reinnervation outcomes of postoperative-ES vs. CES. **Objective:** To compare axonal outgrowth and sensorimotor reinnervation outcomes follow CES, postoperative-ES, or both in a rat tibial nerve injury model. **Methods:** Sprague Dawley rats were equally divided into four cohorts: i) CES, ii) postoperative-ES, iii) CES + postoperative-ES, and iv) sham. CES was delivered one week prior to nerve cut/coaptation while postoperative-ES was delivered immediately following coaptation. Length of nerve regeneration was assessed at 7-days post-repair (n=6), and physiological and behavioural testing were performed at 7-weeks post-coaptation (n=4). **Results:** Animals treated with CES alone had significantly longer lengths of

regeneration and sensorimotor reinnervation compared to all other cohorts. One-week post-injury, CES-treated axons extended 8.5 ± 0.6 mm, significantly longer than in the postoperative-ES (3.6 ± 0.3 mm), CES + postoperative-ES (5.5 ± 0.5mm), or sham (2.7± 0.3 mm). Sensory reinnervation was significantly better in the CES group, with greater sensitivity to Von Frey filaments and a higher density of intraepidermal nerve fibers compared to all other cohorts ($p<0.001$). Similarly, motor reinnervation, evaluated using behaviour (width of toe spread, performance on the horizontal ladder test), electrophysiological (CMAP amplitude) and immunohistochemistry (reinnervated neuromuscular junctions) were all significantly better in the CES cohort ($p<0.001$). **Conclusion:** CES significantly improves regeneration and reinnervation beyond that attainable with current clinical standard using postoperative ES. It is a clinically feasible method of improving outcomes for patients with peripheral nerve injury. Further investigation is required to delineate molecular and cellular mechanisms associated with each treatment modality.

Disclosures: C.A. Webber: None. **J. Senger:** None. **H. Macandili:** None. **A. Chan:** None. **K. Chan:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.03/CC6

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS057190

Title: Axon regeneration is enhanced in the absence of asparagine endopeptidase (AEP, δ secretase)

Authors: *A. W. ENGLISH[1], K. YE[2]
[1]Dept Cell Biol., [2]Dept Pathol & Lab. Med., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Injuries to peripheral nerves are common but functional recovery from them is poor. Enhancing axon regeneration after nerve injury has emerged as a target for the development of novel therapies to improve functional recovery. Elongation of regenerating axons is produced by the addition of cytoskeletal elements, mainly microtubules and actin filaments, to their distal ends. The axonal microtubule-associated protein, Tau, stabilizes microtubules in regenerating axons. Asparagine endopeptidase (AEP, δ secretase) is a lysosomal cysteine protease that cleaves Tau at N255 and N368 residues and degrades its microtubule-stabilizing function. We used an antibody specific to Tau N368 and enzyme activity assays to show that significant AEP activity and AEP-degraded Tau are found in the distal segments of cut and repaired mouse sciatic nerves. Using mice null for AEP bred on a background of the thy-1-YFP-H mouse, we found that, two

weeks after injury, regenerating axon profiles were more than three times longer in these AEP KO mice than in untreated wild-type (WT) controls and 40% longer than WT mice treated systemically with the small molecule trkB agonist, 7,8 dihydroxyflavone (7,8 DHF). The amplitudes of direct muscle EMG responses (M waves) evoked in gastrocnemius and tibialis anterior muscles by stimulating sciatic nerves proximal to a transection injury were restored more than twice as fast in AEP KO mice as untreated WT controls and comparable to that noted in WT mice treated with 7,8 DHF. The amplitude of M responses recorded 10 weeks after injury in AEP KO mice and WT mice treated with 7,8 DHF was comparable to the pre-transection responses. In untreated WT controls, this value was only 45% of pre-transection controls at that recovery time. Inhibiting AEP activity could be a potent strategy for enhancing axon regeneration and functional recovery after peripheral nerve injury.

Disclosures: A.W. English: None. **K. Ye:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.04/CC7

Topic: C.10. Brain Injury and Trauma

Support: University of Calgary University Research Grants Committe
Alberta Innovates-Health Solutions
University of Calgary Cumming School of Medicine
Hotchkiss Brain Institute Axon Biology and Regeneration Theme Studentship

Title: Pro-inflammatory macrophage phenotype and activation are regulated by CRYAB *in vitro* and after peripheral nerve damage

Authors: *S. S. OUSMAN[1], E.-M. F. LIM[2], V. HOGHOOGHI[2]
[1]Clin. Neurosciences and Cell Biol. & Anat., [2]Neurosci., Hotchkiss Brain Institute, Univ. of Calgary, Calgary, AB, Canada

Abstract: Macrophages play a critical role in creating a supportive environment for regrowing axons following injury to the peripheral nervous system (PNS). Post-PNS damage, de-differentiated Schwann cells (SCs) secrete cytokines and chemokines that promote the recruitment of monocytes to the injured site. These monocytes differentiate into macrophages that produce cytokines that contribute to further recruitment of hematogenous macrophages. Importantly, these blood-derived macrophages phagocytose axonal and myelin debris that are inhibitory to axon growth. The beneficial aspects of immune cells and their secretory products such as cytokines are evident. However, a prolonged inflammatory response after PNS injury has been implicated in the pathogenesis of negative symptoms such as neuropathic pain. Therefore,

the immune response after PNS damage must be carefully controlled to prevent secondary damage while allowing for beneficial regenerative processes to occur. CRYAB is a small heat shock protein that is expressed by PNS axons and SCs. We previously showed that the protein plays a beneficial role in peripheral nerve regeneration by promoting the re-differentiation of, and remyelinating ability of SCs after PNS injury. Due to the extensively reported immunomodulatory role of CRYAB, we investigated whether the small heat shock protein also influences macrophage responses during Wallerian degeneration. Using CRYAB null mice, we found that although the recruitment of macrophages into crushed sciatic nerves was not altered by CRYAB as shown by similar numbers of macrophages and, amount of cytokines and chemokines at 1-7d post-damage between wildtype (WT) and $CRYAB^{-/-}$ mice, there was a sustained presence of macrophages in the injured distal sciatic nerves of $CRYAB^{-/-}$ mice at 21 and 28d post-damage. To determine if CRYAB can affect the phenotype and activation of macrophages, we performed *in vitro* assays whereby macrophages from WT and $CRYAB^{-/-}$ mice that had been polarised to a pro-inflammatory or immunosuppressive phenotype were stimulated with lipopolysaccharide in the presence or absence of recombinant CRYAB and evaluated for the secretion of various cytokines. We found that CRYAB specifically impacts pro-inflammatory but not immunosuppressive macrophages by reducing their cytokine production. We are currently evaluating if the elevated number of macrophages in the injured sciatic nerves of $CRYAB^{-/-}$ mice is skewed towards a particular phenotype. Thus far then, we have found that the small heat shock protein CRYAB plays a role in preventing the prolonged presence of macrophages, possibly of the pro-inflammatory phenotype, after PNS damage.

Disclosures: S.S. Ousman: None. **E.F. Lim:** None. **V. Hoghooghi:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.05/CC8

Topic: C.10. Brain Injury and Trauma

Support: Canadian Institutes of Health Research #142328 to VMKV
Univ of Saskatchewan College of Medicine research awards to BRM

Title: Nerve injury effects rapid mobilization of NGF receptors to the axonal membranes of sensory neurons and increased receptor activation, which can be enhanced by electrical stimulation

Authors: B. R. MCMILLAN, R. ZHAI, J. JOHNSTON, *V. M. VERGE
Anat. & Cell Biol., Univ. Saskatchewan-CMSNRC, Saskatoon, SK, Canada

Abstract: We and others have shown that therapies such as electrical nerve stimulation (ES) accelerate and increase the number of axons regenerating across the injury site, especially at early time points, thereby enhancing the probability that a patient will recover successfully from traumatic peripheral nerve injury (Geremia et al., 2007 Exp Neurol 205(2):347). We also found that small reductions in pH, consistent with that observed following injury, activate proton-sensitive ion channels, depolarize the neuron and effect rapid mobilization of` additional nerve growth factor (NGF) receptors (trkA) to sensory neuron membranes, making them more responsive to NGF (Bray et al., 2013 J Neurosci 33(19): 8202). Given the role of trkA in sensory axon guidance and response to NGF cues following injury (Webber et al., 2008 J Neuropath Exp Neurol 67(3) 212), we posited that the beneficial impacts of ES on regenerating nerves are associated with rapid changes in membrane properties of the axons with respect to the numbers of neurotrophin receptors on the axon surface. Thus, we examined whether brief 60 minute ES (20 Hz) of crush injured sciatic nerves or 20 mM KCl-mediated depolarization of cultured sensory neurons would result in rapid NGF receptor mobilization from intracellular stores to injured axon membranes and increase levels of receptor activation, providing a mechanism to rapidly alter the sensitivity of axons to local neurotrophin growth permissive cues. Using immunohistochemical approaches, preliminary findings reveal that sciatic nerve crush injury in adult male Wistar rats effects a rapid mobilization of the NGF receptor trkA to the axon membrane 60-minute post-injury, with a corresponding higher level of trk activation observed at the injured axon front. This response appeared to be enhanced in the ES-treated group and can be elicited by KCl-induced depolarization of cultured sensory neurons. The ability of increased neural activity to rapidly alter neurotrophin responsiveness in injured axons likely contributes to the improved regenerative events observed in response to ES.

Disclosures: B.R. McMillan: None. **R. Zhai:** None. **J. Johnston:** None. **V.M. Verge:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.06/CC9

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant 5R01EB020050-03

Title: The addition of heat-releasable neurotrophin-3 and chondroitinase ABC to a nerve guidance conduit does not improve compound muscle action potential amplitudes in a rat model of sciatic never repair

Authors: *A. DONSANTE[1], K. E. MCDANIEL[1], N. S. HARDCASTLE[1], D. M. O'CONNOR[1], J. XUE[2], Y. XIA[2], N. BOULIS[1]

[1]Emory Univ., Decatur, GA; [2]The Wallace H. Coulter Dept. of Biomed. EngineeringAtlanta, Georgia Inst. of Technol. and Emory Univ., Atlanta, GA

Abstract: Background: Peripheral nerve injuries are estimated to affect one million people worldwide each year, resulting in loss of motor function, loss of feeling, and/or the development of pain. In cases where the injury results in a substantial gap between the healthy portions of the nerve, an autograft is usually performed to bridge the gap. However, this requires sacrificing a functional sensory nerve, causing loss of feeling and potentially pain in another part of the body. In addition, long gaps are difficult to repair with this approach. Therefore, there is an urgent, unmet need for better tools to mend nerves. In a previous study, we tested the ability of nerve guidance conduits (NGCs) made from electrospun poly(ε-caprolactone) nanofibers to repair the sciatic nerve in a rat model of nerve transection. Animals receiving plain NGCs recovered ~40% of the muscle strength regained by autograft controls. Adding Schwann cells (SCs) differentiated from bone marrow mesenchymal stem cells to the NGCs boosted muscle strength to ~60% of animals receiving autografts.
Study Design: Seeking to further enhance the NGCs, we sought to augment them with two factors: neurotrophin-3 (NT-3) to enhance neurite extension and chondroitinase ABC to degrade inhibitory proteoglycans. These factors were incorporated together with a near infrared (NIR)-sensitive dye (indocyanine green) into microparticles made of phase change material (a eutectic mixture of lauric acid and stearic acid at a ratio of 8:2) which was sandwiched between two layers of electrospun nanofibers, allowing controlled release of the factors through the use of an NIR laser. In the current study, five treatments were compared: an autograft using the excised nerve segment, plain NGCs, NGCs+SCs, NGCs+factors, and NGCs+factors+cells. Each animal was challenged with an 8 mm gap in the sciatic nerve. For conduits containing factors, a NIR laser was externally applied weekly, moving stepwise from the proximal end to the distal end over three weeks.
Results: Twelve weeks after the injury and repair, compound muscle action potentials (CMAPs) were measured in the gastrocnemius muscle. Compared to an autograft, plain NGCs and NGCs+SCs produced CMAP amplitudes of 44% and 58%, respectively. Contrary to our expectations, NGCs+factors and NGCs+factors+cells produced lower CMAP amplitudes (28% and 30% of autografts, respectively). Axon counts, immunohistochemistry for regeneration markers, and analysis of neuromuscular junctions are on-going. The results suggest that the factors or the heat needed to release them have an adverse effect on axonal regeneration.

Disclosures: A. Donsante: None. **K.E. McDaniel:** None. **N.S. Hardcastle:** None. **D.M. O'Connor:** None. **J. Xue:** None. **Y. Xia:** None. **N. Boulis:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.07/CC10

Topic: C.10. Brain Injury and Trauma

Title: Extending the maximum critical nerve gap in the rat sciatic nerve model using curved conduits

Authors: *G. S. BENDALE[1,2], Y. TONG[3], E. SHIMIZU[2], S. ANAND[2], B. N. JOHNSON[3], M. I. ROMERO-ORTEGA[4]
[1]Bioengineering, Univ. of Texas At Dallas, Irving, TX; [2]UT Dallas, Richardson, TX; [3]Virginia Tech., Blacksburg, VA; [4]Bioengineering, Univ. of Texas at Dallas, Richardson, TX

Abstract: Despite the ability of the adult peripheral nervous system to spontaneously regenerate, this process often fails in large nerve defects (i.e., >3 cm), resulting in permanent sensory and motor deficits. The study of regenerative strategies for large gaps, primarily relies on large animal models including rabbits, cats, dogs, and sheep. However, these models offer limited objective measurements of functional recovery. In contrast, the rat sciatic nerve (ScN) model is widely accepted, well characterized, and offers a number of metrics of functional regeneration. However, the maximum gap length in this model is 2 cm. We reasoned that a nonlinear silicone conduit fabricated with a microextrusion 3D printing process could be used to extend the critical nerve gap in the rat ScN. Thus, here, we tested the ability of the ScN to growth through an S-conduit. Ten adult rats were equally divided into two groups for repair of a gap injury: a) straight tubes, 10mm in length and b) S-shaped nerve guides with a path length of 13 mm . All conduits were filled with collagen to facilitate regeneration and implanted between the two ends of the transected nerve. Starting at one-week post-surgery, and weekly for two months, the animals were evaluated for gait analysis using Gait Scan. At the end of the study, electrophysiology was conducted across the gap to verify functional nerve conduction. Gross histology showed no apparent difference between the regenerated nerves in the straight tube compared to the S-shaped conduits. This was confirmed by measurements of average thickness of the regenerated nerves at multiple 2.5 mm segments across the gap, which showed no significant difference between the two groups. Toe-spread index indicated successful functional recovery at week 7 compared to week 1 post-surgery ($P<0.05$). However, no significant differences were noted between the straight guides and the S-shaped conduits at any time point. Histological evaluation of the regenerated tissue immunolabeled with β-III tubulin and protein-0 (P0), to visualize axons and myelin; respectively, showed comparable axonal regeneration in both types of conduits. These results confirmed that injured axons in the ScN grow effectively through curved conduits, opening the possibility of using S-guides to extend the nerve gaps in rats beyond the current 2 cm limit. This method may offer a viable alternative to the use of larger animal models for the test of long gaps repair strategies, while taking advantage of the broad behavioral sensory-motor tests, and biochemical and cell biology techniques, that are well established in the rat model.

Disclosures: G.S. Bendale: None. **Y. Tong:** None. **E. Shimizu:** None. **S. Anand:** None. **B.N. Johnson:** None. **M.I. Romero-Ortega:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.08/CC11

Topic: C.10. Brain Injury and Trauma

Support: NIH R01 NS085167
NIH R01 NS094384

Title: Improving generalization of recovery using vagus nerve stimulation after peripheral nerve injury

Authors: *M. DARROW[1], A. D. RUIZ[2], M. BILAL[5], A. ZALLOUM[5], A. SEYEDA[5], M. SHETH[5], D. PARMAR[5], J. TRAN[5], M. P. KILGARD[3], S. A. HAYS[4]
[1]Texas Biomed. Device Center/Bioengineering, [2]Texas Biomed. Device Ctr., Univ. of Texas At Dallas, Plano, TX; [3]Behavioral and Brain Sci., [4]Bioengineering, Univ. of Texas At Dallas, Richardson, TX; [5]Texas Biomed. Device Ctr., Richardson, TX

Abstract: Although nerve injuries occur in the peripheral nervous system (PNS), dramatic reorganization occurs within the spinal cord, cortex, and subcortical structures following injury. In severe injuries such as transection, axonal sprouting is imprecise and numerous axons fail to reestablish prior connection. Due to the extensive amount of mismatch, natural reorganizational processes are incapable of complete functional recovery. Following injury and surgical repair no more than 50% of human patients regain useful function. Meyers et al. has shown that by enhancing reorganization throughout the CNS by the use of VNS paired with rehabilitation, we can selectively enhance the connectivity of the circuits mediating skilled forelimb use and enhance forelimb recovery. Patients have a limited time to do rehab so it is necessary to optimize VNS delivery during rehab. Patients with upper limb impairments after PNI train on many tasks with the physical therapist or clinician during their rehabilitation. Generalization is important because it determines whether more repeats of a single task should be paired with VNS, or fewer repeats with a variety of tasks. Previously Meyers et al. has shown that VNS benefits generalize after stroke, but it isn't clear if that happens after PNI. This aim will investigate if VNS paired with the isometric pull task can drive recovery on both the isometric pull task and the supination knob tasks simultaneously following peripheral injury. We hypothesize that by pairing VNS with the isometric pull task, VNS benefits will generalize to the supination task. If this hypothesis is incorrect and the VNS benefits do not generalize then it will be informative to understand that VNS may need to be paired with many tasks during rehabilitation or trying to rehabilitate many tasks with VNS therapy at one time may not be beneficial. Our previous results also demonstrate that VNS paired with rehabilitative training enhances functional recovery of forelimb strength. However, the effects of VNS did not last after the cessation of training for one month.

Additionally we will further investigate if VNS therapy effects are long lasting with continued rehabilitation.

Disclosures: M. Darrow: None. **A.D. Ruiz:** None. **M. Bilal:** None. **A. Zalloum:** None. **A. Seyeda:** None. **M. Sheth:** None. **D. Parmar:** None. **J. Tran:** None. **M.P. Kilgard:** None. **S.A. Hays:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.09/CC12

Topic: C.10. Brain Injury and Trauma

Title: *In vivo* non-viral delivery of gene and cell therapies to peripheral and central nervous system

Authors: *J. T. MOORE[1], N. HIGUITA-CASTRO[2], C. WIER[3], A. SUNYECZ[4], R. CHO[5], M. REILLY[2], C. SEN[4], S. J. KOLB[3], D. GALLEGO-PEREZ[2]
[1]Biomed. Engin, [2]Biomed. Engin., [3]Neurol., [4]Surgery, [5]Ophthalmology, Ohio State Univ., Columbus, OH

Abstract: Direct cargo/gene delivery to peripheral nerves has the potential to enable a host of novel therapies to support nerve repair after traumatic injury and/or neuropathies. However, delivery of targeted therapies to nerves remains a challenge. Current delivery methods present significant translational hurdles, including heavy reliance on viral vectors, stochasticity, and tissue damage. This work describes a novel nanochannel-based platform for non-viral transfection of nerves *in vivo* in a fast (100 ms), highly efficient and benign manner. Nanochip platforms containing an array of nanopores were fabricated using cleanroom-based fabrication techniques and used to precisely nanoporate and deliver desired molecular cargo into nerve tissue via electrophoresis. We have successfully applied this technology for transfection of the sciatic nerve (SN) in a mouse model to deliver reprogramming angiogenic factors as a potential therapeutic strategy to aid axonal growth and nerve repair. Scalability of this intervention was assessed by transfecting the optic nerve (ON) of pigs with fenestrated and non-fenestrated dura mater. Transfection efficiency and retrograde transport to the PNS and CNS was assessed via immunofluorescence microscopy and qRT-PCR after transfection. Successful nerve transfection was observed in tissue sections collected 24 hours to 7 days after transfection. Cargo delivery extended beyond the initial transfection boundary (epineurium) into the endoneurium. One week after transfection with angiogenic reprogramming factors, we observed nerve stroma reprogramming into vascular tissue as evidenced by increased expression of CD31 in close proximity with axonal processes along the entire length of the nerve. Upstream tissue analysis after SN transfection revealed that tailoring the transfection conditions resulted in the delivered

gene cargo reaching the dorsal root ganglion (DRG) and ventral horn of the spinal cord (SC). Immunofluorescence analysis confirmed successful tissue transfection and strong pro-endothelial gene activity at the SN, DRG and SC levels with no appreciable behavioral changes (*e.g.*, paw clenching, gait perturbations). Pilot experiments in the optic nerve of pigs indicated successful cargo delivery as well as strong gene expression across the entire nerve cross-section. This study supports the feasibility of non-viral gene delivery to nerves as a tool to enhance nerve regeneration following a focal injury. Moreover, retrograde delivery to the CNS from peripheral nerves expands the potential applicability of our method to the treatment of focal CNS insults.

Disclosures: J.T. Moore: None. **N. Higuita-Castro:** None. **C. Wier:** None. **A. Sunyecz:** None. **R. Cho:** None. **M. Reilly:** None. **C. Sen:** None. **S.J. Kolb:** None. **D. Gallego-Perez:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.10/CC13

Topic: C.10. Brain Injury and Trauma

Support: MOST106-2314-B-182 -029 -MY3

Title: Lithium attenuates diabetic neuropathic pain through augmentation of spinal glycinergic inhibitory control

Authors: *C.-R. LIN[1], W.-T. LIAO[2], C.-L. TSAI[3]
[1]Kaohsiung Chang Gung Mem. Hosp. and Chang Gung Univ. Col. of Medi, Niao-Sung District, Taiwan; [2]Chia-Yi Chang Gung Mem. Hosp., Chia-Yi, Taiwan; [3]Anesthesiol., Kaohsiung Chang Gung Mem. Hosp. and Chang Gung Univ. Col. of Medi,, Kaohsiung, Taiwan

Abstract: Lithium is an effective medication for the treatment of bipolar affective disorder. Accumulating evidence suggests that inflammation plays a role in the pathogenesis of neuropathic pain and that lithium has anti-inflammatory effects that may contribute to its therapeutic efficacy. However, the effects and mechanisms of lithium on diabetic lithium affect neuropathy remain unknown. The present study examined the effect of locally injected lithium on neuropathic pain induced by streptozotocin.Male Sprague-Dawley rats with or without streptozotocin intraperitoneal injections were used. Tactile sensitivities were assessed by measuring paw withdrawal thresholds to von Frey filaments for four weeks. The extent of GlyR-mediated inhibition controlling primary afferent-evoked excitation in dorsal horn neurons was examined by using the whole cell patch clamp recording technique in isolated adult rat spinal cord slices. The content of the spinal dorsal horn glycine levels was measured by microdialysis. We found that persistent hyperglycemia induced by the administration of STZ caused a decrease

in the paw withdrawal latency to mechanical stimuli. The miniature inhibitory post-synaptic current (mIPSC) rise, decay kinetics and mean GlyR-mediated mIPSC amplitude were not affected in DNP. The mean frequency of GlyR-mediated mIPSC of lamina I neurons from DNP rats was, however, significantly reduced when compared with neurons from control rats. Principal passive and active membrane properties and the firing patterns of spinal lamina I neurons were not changed in DNP rats. Spinal microdialysis rats had a significantly decreased glycine level following its initial elevation. Intraplantar administration of lithium diminished tactile pain hypersensitivity and attenuated decreased level of glycine in DNP rats. In conclusion, these results indicate that long-lasting hyperglycemia induced by STZ injections leads to a reduced glycinergic inhibitory control of spinal lamina I neurons. Intraplantar lithium administration partially reversed tactile hypersensitivity and reduced glycinergic inhibitory control.

Disclosures: C. Lin: None. **W. Liao:** None. **C. Tsai:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.11/CC14

Topic: C.10. Brain Injury and Trauma

Support: JSPS KAKENHI for H. Kanemaru (15K20509)
JSPS KAKENHI for K. Seo (15H05041E)

Title: Involvement of vascular endothelial growth factor in regeneration of injured inferior alveolar nerve

Authors: *Y. NISHIDA[1,2], Y. YAMADA[3], H. KANEMARU[2], T. MAEDA[3], A. OHAZAMA[4], K. SEO[2]
[1]Niigata Univ. Grad. Sch. of Med. and, Niigata, Japan; [2]Dent. anesthesiology, [3]Ctr. for Advanced Oral Sci., [4]Oral Anat., Niigata Univ. Grad. Sch. of Med. and Dent. Sci., Niigata, Japan

Abstract: Introduction The activation of vascular endothelial growth factor (VEGF), a regulator of angiogenesis and vascular permeability, has been reported in damaged neuron. This molecule can induce neurotropic/neuroprotective functions in injured neuron by regaining of oxygen/nutrition supply from blood circulation. However, little information is available for the role of endogenous VEGF in the regeneration of peripheral nerves following injury. Aims The present study was undertaken to examine the function of endogenous VEGF on regeneration of damaged inferior alveolar nerve (IAN). In addition, we clarified the existence of VEGF receptor and the secretion mechanism during regeneration process. Material and methods This study used the IAN injured animal model of injured IAN which we have previously reported (Yamada et al.,

2018). Briefly, under deep anesthesia, the exposed IAN was resected and left apart with an interval of 0.5mm between the cut ends. The animals were sacrificed at post-operative day (PO) 1, 2, 3, 5 and 7. Some mice received a local administration of anti-VEGF antibody (1µg per day) at every 24 hours for 5days after operation. Observations focused on 1) the chronological changes in regeneration of axons and blood vessels, 2) the chronological changes in expression pattern of VEGF receptor 1 during damaged IAN regeneration, 3) the effects of local administration of anti-VEGF antibody on nerve regeneration process at PO day 7 by immunohistochemistry for PGP9.5, and 4) the invasive status of macrophages to the transection site at PO day 2. Results Current observations showed; 1) Blood vessels began to sprout into transection site at PO day 2 prior to the axonal regeneration. 2) The proximal stamp of the transected IAN expressed strong VEGFR1 at PO day 3. 3) A local administration of anti VEGF significantly suppressed the axonal growth. 4) Macrophages invaded in the proximal stump of the transected IAN at PO day 2. Expression of VEGF receptor and accumulation of macrophage appeared at the medial site of the damaged nerve immediately after the injury. Conclusions The present findings suggested the induction of local VEGF secretion by nerve damages. VEGF-VEGF receptor system may contribute to facilitate regeneration of axonal elongation from injured site as well as to re-establish micro-vascularization. Supported by JSPS KAKENHIs for H. Kanemaru (15K20509) and K. Seo (15H05041E)

Disclosures: Y. Nishida: None. **Y. Yamada:** None. **H. Kanemaru:** None. **T. Maeda:** None. **A. Ohazama:** None. **K. Seo:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.12/CC15

Topic: C.10. Brain Injury and Trauma

Support: RA205018PAPIIT

Title: Effectiveness of portland cement on the repair of inferior dental nerve in mice C57bl/6

Authors: *M. VIVEROS SANCHEZ[1], A. L. GARCIA-HERNANDEZ[2], I. O. PEREZ-MARTINEZ[3]
[1]UNAM, Mexico, Mexico; [2]Lab. of Oral Inmunology and Osseous Regulation, Cuautitlán Mexico, Mexico; [3]Lab. of Neurobio. of Oral Sensations, Cuautitlán Mexico, Mexico

Abstract: Chronic neuropathic pain can be produced by injuries on peripheral nerves, superficial or deep damages under periapical areas of the teeth could hurt inferior dental nerve causing chronic pain and having negative repercussions at cognitive and emotional levels, decreasing people's life quality. Materials like Portland cement can be used for bone defects, because it has

osteogenic properties and anti-inflammatory effects reducing it; however, it is not known the consequences in the trigeminal damage in its intraosseous branch.
Objective: determinate the effectiveness of Portland cement on the repair of the exposed inferior dental nerve in a mandibular lesion.
Method: 12 mice C57bl/6 were used, divided in 3 groups: 1. Control, 2. Osseous lesion with exposed nerve and 3. Osseous lesion with exposed nerve treated with Portland cement. Presence of spontaneous pain was evaluated with the grooming behavior at -2,2,4,6 and 8 days. Affective component to induced pain was characterized using the place escape/avoidance paradigm at -1,1,3,5, and 9 days. Expression of pro-inflammatory cytokines IL-6 and TNF-α were determinate with ELISA assay at 3rd day. Three days after surgery the mice´s jaws were prepared for sectioning, serial sections (4µm thickness) was made and dyed with Hematoxylin and Eosin for histological observations.
Results: experimental group show a major hyperalgesia responds at days 5 and 7 (ANOVA $p<0.05$), there are significative differences in the presence of spontaneous pain in the groups with osseous lesion with exposed nerve against control group and experimental at 6 and 8 days (ANOVA < 0.05).
Conclusion: Portland cement decreases spontaneous pain however it can induce a peripherical sensitization when it is used like a therapeutic option in an osseous mandibular lesion with nerve exposure.
This project was supported by PAPIIT RA205018
Correspondence to
Isaac O. Perez-Martinez, PhD
e-mail: Isaac.perez@campus.iztacala.unam.mx
Laboratory of neurobiology of oral sensations
CUSI ALMARAZ planta baja. A. Jiménez Gallardo SN Sn. Sebastián Xhala 54714 Cuautitlán Mexico

Disclosures: M. Viveros sanchez: None. **A.L. Garcia-Hernandez:** None. **I.O. Perez-Martinez:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.13/CC16

Topic: C.10. Brain Injury and Trauma

Support: PAPITT-UNAM IN 212916 to MMG

Title: Effective neuromodulation of pelvic floor nerves despite damage induced by multiparity and aging in incontinent rabbits

Authors: *A. G. HERNANDEZ-REYNOSO[1], K. LÓPEZ-GARCÍA[3], R. ZEMPOALTECA[4], D. L. CORONA QUINTANILLA[5], F. CASTELÁN[6], M. I. ROMERO-ORTEGA[2], M. MARTINEZ-GOMEZ[7]
[1]Bioengineering, Univ. of Texas at Dallas, Plano, TX; [2]Bioengineering, Univ. of Texas at Dallas, Richardson, TX; [3]CTBC, Dpto. Biología Celular y Fisiología, [4]CTBC, Dpto. Biologia Celular y Fisiologia, Inst. de Investigaciones Biomedicas, UNAM, Tlaxcala, Mexico; [5]Univ. Autónoma de, Tlaxcala, Mexico; [6]Inst. de Investigaciones Biomedicas, Univ. Nacional Autonoma de Mexico, Tlaxcala, Mexico; [7]Inst. de Investigaciones Biomédicas UNAM, Tlaxcala, Mexico

Abstract: Pelvic floor muscles (PFM) provide organ support and participate in urinary and fecal continence as extrinsic closure mechanisms. Their dysfunction is involved in disorders including urinary incontinence (UI), a condition that affects 30-60% of the female population and 5-15% of males. Risk factors such as pregnancy cause stretch injury of the PFM, and aging weakens it. This damage can be either myogenic or neurological. Female rabbits have a well-developed pelvic floor and similar activity patterns to those observed in women. Additionally, vaginal birth and aging also result in UI symptoms in this animal model. We recently observed that the bulbospongiosus and the pubococcygeus nerves are partially compromised in multiparous rabbits, and that evoked compound action potentials in response to electrical stimulation were reduced in amplitude suggesting partial neurological dysfunction. Here we use electron microscopy to further define the neural damage in the pelvic floor nerves of young (1-2 years old) and old (3-4 years old) rabbits, either nulliparous or multiparous. Histomorphometric analysis showed that the number of large diameter axons in aged multiparous animals (4.46 ± 1.84 per 1000 μm^2) were comparable to those in nulliparous rabbits (5.21 ± 1.54 fibers per 1000 μm^2). We noted that the axons in the old multiparous animals were abnormally elliptical in shape. Quantitative analysis of axon roundness, estimated by the short over the long diameter ratio, show that axons in old animals were 35% more elliptical compared to young rabbits ($p<0.001$) suggestive of compression injury. We also observed injured axons undergoing Wallerian degeneration, some with abnormal myelin morphologies, including thick myelin, wide Schmidt-Lanterman incisures, and thin myelin on large axons, suggestive of re-myelination. Further analysis revealed that the g-ratios were not affected by parity, but were reduced approximately 25% in aging animals, with a characteristic degenerative invagination of the myelin sheath. We estimated the tortuosity of the myelin folding by dividing the myelin perimeter of the fiber over the calculated perimeter of a perfect ellipse of the same dimensions, and observed an estimated 20% increase in myelin tortuosity in old animals. Damage by multiparity involves Wallerian degeneration that re-myelinates spontaneously, which is exacerbated in old animals resulting in more prominent myelin defects. However, since most of the nerve fibers remain normal, we tested the effect of electrical stimulation of the PFM nerves as a strategy to modulate urodynamic parameters in this animal model. Evidence of effective neuromodulation of UI will be presented.

Disclosures: A.G. Hernandez-Reynoso: None. **K. López-García:** None. **R. Zempoalteca:** None. **D.L. Corona Quintanilla:** None. **F. Castelán:** None. **M.I. Romero-Ortega:** None. **M. Martinez-Gomez:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.14/DD1

Topic: C.10. Brain Injury and Trauma

Support: NIH R01 NS085167
NIH R01 NS094384

Title: Restoring central networks improves motor and sensory function after nerve damage

Authors: *E. MEYERS, N. KASLIWAL, E. LAI, M. ROMERO-ORTEGA, R. RENNAKER, M. KILGARD, S. HAYS
Univ. of Texas At Dallas, Richardson, TX

Abstract: Damage to the peripheral nervous system is common and results in debilitating, chronic loss of motor and sensory function. Directing plasticity within spared and reconnected circuits represents an avenue to restore function long after injury. Here, we describe a novel closed-loop neuromodulation strategy using precisely-timed vagus nerve stimulation (VNS) paired with rehabilitative exercises to facilitate neural plasticity. VNS paired with rehabilitation more than doubled recovery of forelimb motor function and somatosensation compared to equivalent rehabilitation alone after transection of the median and ulnar nerves in rats. In conjunction with functional recovery, VNS enhanced descending motor output and synaptic connectivity in motor networks selectively controlling the denervated muscles and reversed maladaptive non-selective muscle synergies. Recovery persisted after the cessation of VNS therapy because connectivity in central networks was restored. Manipulations that blocked plasticity in central networks prevented VNS-dependent recovery. Building on the clinical record of safety and ease of implementation, this VNS-based targeted plasticity strategy represents a readily translatable method to substantially improve motor and sensory function in patients suffering from nerve damage.

Disclosures: E. Meyers: None. **N. Kasliwal:** None. **E. Lai:** None. **M. Romero-Ortega:** None. **R. Rennaker:** None. **M. Kilgard:** None. **S. Hays:** None.

Poster

665. Brain Injury and Trauma: Peripheral Nerve Trauma, Crush, and Toxic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 665.15/DD2

Topic: C.10. Brain Injury and Trauma

Support: NINDS; R01NS086818

Title: Focal reduction of monocarboxylate transporter 1 (MCT1) in macrophages delays peripheral nerve regeneration

Authors: *M. K. JHA[1], F. YANG[1], C. XUE[1], Y. LEE[1,2], A. HOKE[1], J. D. ROTHSTEIN[1], B. M. MORRISON[1]
[1]Johns Hopkins Univ., Baltimore, MD; [2]Dept. of Biomed. Sci., City Univ. of Hong Kong, Hong Kong, China

Abstract: The remarkable regenerative capacity of the peripheral nervous system (PNS) requires a high metabolic energy demand. Traumatic nerve injury triggers a cascade of events that culminate in a robust infiltrating macrophage-dependent inflammatory reaction, which is indispensable to normal progression of Wallerian degeneration and regeneration. However, the metabolism of macrophages in peripheral nerve regeneration has not yet been explored. We had previously published that reducing the primary lactate transporter in the peripheral nerve, monocarboxylate transporter (MCT1), by half in all cells dramatically delayed nerve regeneration. Through careful analysis of cell-specific deletion of MCT1, we have now determined that downregulation of MCT1 only in macrophages leads to a similar delay in nerve regeneration following injury, as measured by nerve electrophysiology and histology. Evaluating MCT1-deficient macrophages *in vitro* suggests that the delayed nerve regeneration in mice *in vivo* is due to impaired energy production in macrophages, since they have weakened capacity for both mitochondrial oxidative phosphorylation and glycolysis. Additionally, classic pro-inflammatory cytokines are increased, while pro-regenerative cytokines are reduced, in MCT1-deficient macrophage cultures, potentially disrupting their capacity to facilitate nerve regeneration. Detailed bioenergetic and functional evaluations of macrophages with and without MCT1 and potential implications to the process of nerve regenerations are ongoing. We have also begun to evaluate nerve regeneration in transgenic mice with focal upregulation of MCT1 in macrophages as a potential novel therapeutic pathway for accelerating peripheral nerve regeneration.

Disclosures: M.K. Jha: None. **F. Yang:** None. **C. Xue:** None. **Y. Lee:** None. **A. Hoke:** None. **J.D. Rothstein:** None. **B.M. Morrison:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.01/DD3

Topic: D.03. Somatosensation: Pain

Support: ANR JOINT-PAIN

Title: Role of ASIC channels in mouse models of painful diabetic neuropathy

Authors: *J. NOEL, A. NEGM, K. STOBBE, E. DEVAL, E. LINGUEGLIA, C. ROVERE
IPMC, CNRS UMR7275, 06560 Valbonne, France

Abstract: Acid-Sensing Ion Channels (ASICs) are depolarizing cationic excitatory channels activated by tissue acidosis. ASIC channels are formed by the trimetric association of ASIC1 to ASIC3 subunits. They are largely expressed throughout the nervous system. In mice, ASIC3 is expressed in Dorsal Root Ganglion (DRG) neurons of small diameters responsible for pain perception. We have previously demonstrated the role of ASIC3 in inflammatory pain. We have shown that ASIC3 channel are activated by moderate tissue acidosis, as low as pH 7.0, and lipids, such as lysophosphatidylcholine (LPC) and arachidonic acid (AA), found at high concentrations in inflammatory exudates. Interestingly, LPC and AA are activators of ASIC3 at physiological pH 7.4, and subcutaneous injection of LPC and AA in mice hind paw induces pain that is dependent on ASIC3 channel. We are now using ASIC3 specific pharmacological tools and venom toxins, and ASIC3 transgenic mice to investigate the role of ASIC channels in diet induced painful diabetic neuropathy. We are using behavioral experiments to measure thermal, mechanical and chemical pain in diabetic mice using radian heat Hargreaves, dynamic von Frey, and nocifensive formalin tests. Electrophysiological approaches including patch-clamp techniques on DRG neurons and skin-saphenous nerve preparation allows us to study the consequences of diabetes on peripheral sensory neurons activity.
In diabetic mice, we found a deregulation of glucose homeostasis independent of the activity or expression of ASIC3 channel. Diabetic mice have a long lasting thermal hypersensitivity that is dependent on ASIC3 channel activity. We are now deciphering the role of ASIC3 channel in response to inflammatory mediators in the nociceptive neuraxis in the thermal hypersensitivity associated with diabetic conditions.

Disclosures: J. Noel: None. **A. Negm:** None. **K. Stobbe:** None. **E. Deval:** None. **E. Lingueglia:** None. **C. Rovere:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.02/DD4

Topic: D.03. Somatosensation: Pain

Title: Neuropathy-associated Nav1.7 variant, I228M causes energy deficit and impairs neurite integrity of DRG neurons

Authors: *S.-I. LEE[1,2], J. G. J. HOEIJMAKERS[3], C. G. FABER[3], I. S. J. MERKIES[3,4], G. LAURIA[5,6], S. G. WAXMAN[1,2]
[1]Dept. of Neurol., Yale Univ. Sch. of Med., New Haven, CT; [2]Ctr. for Neurosci. and Regeneration Res., Veterans Affairs Connecticut Healthcare Syst., West Haven, CT; [3]Dept. of Neurol., Maastricht Univ. Med. Center+, Maastricht, Netherlands; [4]Dept. of Neurol., St. Elisabeth Hosp., Willemstad, Curaçao; [5]Neuroalgology Unit, IRCCS Fndn. “Carlo Besta” Neurolog. Inst., Milan, Italy; [6]Dept. of Biomed. and Clin. Sci. "Luigi Sacco", Univ. of Milan, Milan, Italy

Abstract: Small fiber neuropathy (SFN) is characterized by injury to small-diameter peripheral nerve axons and loss of intraepidermal nerve fibers (IENF). Although available data suggest that SFN results from axonal degeneration and reduced regenerative capacity, the mechanism underlying those dysfunctions are poorly understood.
Gain-of-function variants in sodium channel NaV1.7 that increase firing frequency and spontaneous firing of dorsal root ganglion (DRG) neurons have recently been identified in 5-10% of patients with idiopathic SFN. In our previous in vitro study, DRG neurons transfected with those SFN-associated channel variants displayed reduced neurite length, suggesting that enhanced sodium channel activity can contribute to a decrease in length of peripheral sensory axons.
The activities of ion channels can disturb ionic gradients across the plasma membrane, and neurons consume ATP to maintain ionic homeostasis. Although a high mitochondrial density enables neurons to cope with that energetic challenge, the activities of normal (wild-type) voltage-gated sodium channels can contribute to growth impairment and degeneration of DRG neurites under metabolically challenging conditions.
Conversely, we have hypothesized that enhanced sodium channel activity due to gain-of-function mutations can trigger sustained sodium influx and then result in an energetic deficit in neurons. Therefore, we suggested that the energy deficiency contributes to the impairment of neurite integrity in DRG neurons and degeneration and loss of nerve fibers in SFN.
In the present study, to determine whether SFN-associated Nav1.7 variants can cause ATP deficit, we established a method to measure ATP level in live cells by using FRET technique and examined the effect of a SFN-associate variant NaV1.7 channel, I228M, on the ATP level in

sensory neurons. At 3 days after culturing, DRG neurons transfected with I228M channels exhibited a marked reduction in ATP level at the soma compared to cells expressing wild-type channels. When the culture was subjected to glucose starvation, the neurites expressing I228M showed more rapid ATP reduction, compared to wild-type channels. Our experiments suggest that expression of I228M mutant channels generates an energetic burden in cells as reflected by decreases in ATP level. This could contribute to impaired neurite integrity of DRG neurons transfected with SFN-associated Nav1.7 variants.
We are currently investigating ways to metabolically reverse the ATP deficit induced by the Nav1.7 variant and will determine whether these maneuvers protect against the impairment of neurite integrity in DRG culture and IENF loss in animal models.

Disclosures: S. Lee: None. **J.G.J. Hoeijmakers:** None. **C.G. Faber:** None. **I.S.J. Merkies:** None. **G. Lauria:** None. **S.G. Waxman:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.03/DD5

Topic: D.03. Somatosensation: Pain

Support: University of Minnesota Academic Health Center Faculty Development Grant #16.08

Title: Mouse models of diabetic neuropathy: Decreased K_{ATP} channel expression and function in the peripheral and central nervous system

Authors: *A. H. KLEIN[1], C. FISHER[1], J. L. JANECEK[2], M. L. GRAHAM[2]
[1]Pharm. Practice and Pharmaceut. Sci., Univ. of Minnesota Duluth, Duluth, MN; [2]Dept. of Surgery, Univ. of Minnesota, St. Paul, MN

Abstract: Major complications from T2DM include diabetic neuropathy, which affect many adults with prediabetes and new-onset diabetes. It is clear that novel biomarkers and pharmaceutical targets are needed in order to confront the demand for new treatments that better manage diabetic neuropathy. There is a need for increased knowledge in how diabetes affects structural and molecular changes in the nervous system to lead to the progression of chronic pain. It is assumed that chronic hyperglycemia results loss of sensitivity to K_{ATP} channel blocking drugs (e.g. sulfonylureas) and decreased K_{ATP} channel expression in the central nervous system, which could indicate a widespread decrease in K_{ATP} channel function. K_{ATP} channel subtypes are located in the nervous system and already have implications in pain signaling, including mu opioid receptor signaling. Loss of K_{ATP} channel activity or function could cause nerve fiber hypersensitivity and consequently increased pain sensitivity due to neuron depolarization. In order to answer these questions, diabetic neuropathy was induced in male and

female C57Bl6 mice over a total of 16 weeks by feeding the animals a high-fat diet (HFD) or corresponding control diet (12330 and 12328, Research Diets Inc., New Brunswick, NJ) for over 16 weeks. Mice on the HFD for at longer than 8 weeks have significantly higher circulating C-peptide and insulin levels, higher thermal thresholds, and lower mechanical thresholds and compared to control diet mice. Mice fed a HFD also have decreased analgesia to systemic morphine (0-20 mg/kg, s.c.), which is exacerbated after systemic treatment with glyburide or nateglinide for four weeks, (KATP channel antagonist, glyburide or nateglinide, 50 mg/kg/day, IP or vehicle, 5% DMSO + 0.5% Tween). Decreased expression of KATP channel subunits Kncj8 (Kir6.1) and Abcc9 (SUR2) were found in the spinal cord, while Kcnj11 (Kir6.2) and Abcc8 (SUR1) were decreased in dorsal root ganglia. Sciatic nerves were harvested and electrical thresholds were measured using C-fiber compound action potentials (C-CAPs). C-CAPs from HFD mice had significantly higher electrical thresholds and significantly longer latencies than C-CAPs from control diet mice, which was also exacerbated after systemic treatment with glyburide or nateglinide for four weeks. We conclude that K_{ATP} channels are therefore a promising target to treat the progressive development of diabetes. Further investigation of KATP channel expression and function during chronic pain syndromes, including diabetic neuropathy, may help to find sufficient treatment options for patients.

Disclosures: A.H. Klein: None. **C. Fisher:** None. **J.L. Janecek:** None. **M.L. Graham:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.04/DD6

Topic: D.03. Somatosensation: Pain

Title: Participation of the trek1 potassium channel in neuropathy-induced mechanical hypersensitivity

Authors: *K. MENDEZ RESENDIZ[1], J. MURBARTIAN[2]
[1]CINVESTAV, Mexico, Mexico; [2]Cinvestav, Sede Sur, Mexico, DF, Mexico

Abstract: Dysregulated ion channel function in response to nerve injury results in enhanced neuronal excitability that underlies neuropathic pain. TWIK-related 1 potassium channel (TREK-1) is member of the two-pore domain potassium channel family that contribute to background conductances. TREK-1 channel is modulated by a variety of different physical and chemical stimuli (mechanical, temperature, intracellular acidification, poly-unsaturated fatty acids and phospholipids). TREK-1 activity is regulated in the C-terminal region of the channel by phosphorilation induced by G-protein coupled receptors activation. Nociceptors express TREK-1 channel, and this channel contributes to nociception in inflammatory pain models. However, the role of TREK-1 channel in neuropathic pain remains unclear. The aim of the present

investigation was to determine the participation of TREK-1 in the *mechanical* hypersensitivity induced by a neuropathic pain model in rats. All experiments were performed on adult female Wistar rats. Neuropathic pain was induced by L5/L6 spinal nerve ligation. Tactile allodynia was evaluated at 7 days after surgery. Drugs were administrated intrathecally. TREK-1 expression in the dorsal root ganglia (DRG) was determined by western blot. Spinal nerve ligation produced tactile allodynia from day 1 to 21 after the surgery. Moreover, TREK-1 protein expression increased in DRG (L4/L5) at 7 and 14 days after injury. Intrathecal injection of BL-1249 (TREK-1 activator, 1-100 μM), but not vehicle, reduced in a dose-dependent manner established tactile allodynia. Furthermore, intrathecal injection of Spadin (TREK-1 specific blocker, 1-10 μM) reduced BL-1249 (100 μM) antiallodynic effect in neuropathic rats. In addition, Spadin produced tactile allodynia in a dose-dependent manner in naïve rats. Results obtained suggest that TREK-1 has an antiallodynic effect in neuropathic rats. Furthermore, TREK-1 basal activity is responsible to keep background conductance that does not allow to development of pain in naïve rats.

Disclosures: K. Mendez Resendiz: None. **J. Murbartian:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.05/DD7

Topic: D.03. Somatosensation: Pain

Support: NIH GM120844
NIH DE022015
the N.G. and Helen T. Hawkins Endowment

Title: RE1 silencing transcription factor (REST) mediates nerve injury-induced downregulation of cholinergic receptor muscarinic 2 in primary sensory neurons

Authors: *J. ZHANG, S.-R. CHEN, H. CHEN, H.-L. PAN
Anesthesiol. & Perioperative Med., Univ. of Texas MD Anderson Cancer Ctr., Houston, TX

Abstract: Chronic neuropathic pain disrupts quality of life for many patients. Although persistent changes in gene transcription account for the long-lasting abnormal neuronal excitability, the transcriptional mechanisms involved remain unclear. The muscarinic cholinergic receptors (mAChRs) are tonically involved in the regulation of pain. Here we show that the expression level of cholinergic receptor muscarinic 2 (encode by *Chrm2*) is suppressed in the dorsal root ganglia (DRG) after peripheral nerve injury. Interestingly, the silenced gene expression of *Chrm2* is mediated by RE1 silencing transcription factor (REST; also known as neuron-restrictive silencing factor, NRSF), a transcription repressor. Nerve injury increases

REST gene expression in the rat DRG and promotes the occupancy of REST to the RE-binding site located in the *Chrm2* promoter region. *In vitro* promoter luciferase assay confirms the inhibitory function of RE-binding site for *Chrm2* expression. Knockdown of *Rest* in the rat DRG by siRNA or conditional genetic ablation of *Rest* in DRG neurons restores *Chrm2* gene expression reduced by nerve injury and augments the analgesic effect of muscarine on neuropathic pain. In addition, siRNA knockdown of *Rest* in the rat DRG or conditional knockout of *Rest* in DRG neurons enhances the inhibitory effect of muscarine on synaptic glutamate release from primary sensory nerve terminals to the spinal dorsal horn. Together, our findings support that REST is critically involved in the gene expression level of *Chrm2* in the DRG in neuropathic pain. REST may be targeted to enhance the analgesic effect of muscarinic drugs for in treating neuropathic pain. Of note, our finding may also be relevant to the mechanism of Alzheimer's disease because increased REST and decreased *Chrm2* expression occur in the brains of patients with Alzheimer's disease.

Disclosures: J. Zhang: None. **S. Chen:** None. **H. Chen:** None. **H. Pan:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.06/DD8

Topic: D.03. Somatosensation: Pain

Title: HMGB1 redox isoforms selectively activate neurons and modulate pain-like behavior

Authors: *Q. ZENG[1], M. ADDORISIO[1], M. GUNASEKARAN[1], S. CHAVAN[1], U. ANDERSSON[2], K. TRACEY[1], H. YANG[1]
[1]Feinstein Inst. For Med. Res., Manhasset, NY; [2]Ctr. for Mol. Med., Karolinska Univ. Hosp. Solna, Stockholm, Sweden

Abstract: Pain involves nociception and pathophysiological reactions. Besides neuronal stimulation, nociception can be activated in a milieu of damage-associated molecular pattern (DAMPs) molecules. Among the DAMPs, HMGB1 released following nerve injury has been implicated in mediating the pathogenesis of neuropathic pain (Calvo M, Lancet Neurol 2012; Karatas H, Science 2013). HMGB1 directly acts on nociceptors to induce allodynia as well as to enhance pain-like response mediated by other factors. HMGB1 contains 3 cysteine residues and their redox states generate 3 isoforms of HMGB1 each with different biological functions. Fully reduced HMGB1 induces chemotactic responses; disulfide (mild oxidation) HMGB1 is cytokine-inducing and pro-inflammatory; and sulfonyl (all cysteine residues) HMGB1 has no known immune function (Andersson U, Seminars in Immunol, 2018). The role of isoforms of HMGB1 in neuropathic pain is unknown. Here we aimed to elucidate the effects of 3 isoforms of HMGB1 on neuronal activation and for inducing pain-like behavior. Using calcium mobilization as a

measurement of neuronal excitability, we observed the fluorescence changes / baseline fluorescence before stimulus ($\Delta F/F_0$) in sensory neuron-like F11 cells. Administration of disulfide HMGB1 elicited an intracellular calcium flux ($\Delta F/F_0 = 1.14 \pm 0.06$*), to a less extent by using fully reduced HMGB1 ($\Delta F/F_0 = 0.44 \pm 0.04$*), and further diminished with sulfonyl HMGB1 ($\Delta F/F_0 = 0.26 \pm 0.02$), (*: $p<0.05$ vs. sulfonyl HMGB1). Similar results were observed in sensory neurons isolated from dorsal root ganglia. To test whether the redox state of HMGB1 differentially modulates pain-like behavior *in vivo*, mechanical nociceptive threshold responses were analyzed in SD rats after administration of 3 isoforms of HMGB1 in a hindpaw. Compared to vehicle control, hindpaw injection of disulfide HMGB1 evoked mechanical hyperalgesia in a dose-dependent manner (threshold response (gm) of vehicle = 4.1 ± 0.4, 2 µg/paw = 3.8 ± 0.6; 12 µg/paw = 2.3 ± 0.2*; 20 µg/paw = 1.9 ± 0.2*. n=6 or 12 rats per group, *: $P<0.05$ *vs.* vehicle group). In contrast, neither fully reduced HMGB1 nor sulfonyl HMGB1 provoked any significant effect. Systemic administration of neutralizing anti-HMGB1 monoclonal antibodies (mAb) alleviated these hyperalgesic effects induced by disulfide HMGB1 (threshold response (gm) of vehicle-treated = 4.9 ± 1, HMGB1 + IgG = 1.9 ± 0.3, HMGB1 ± mAb = 3.3* ± 0.3. *: $P<0.05$ *vs.* HMGB1 + IgG), indicating that the hyperalgesia amelioration effects were HMGB1 specific. Taken together, these results suggest that disulfide HMGB1-targeted therapy has a potential as a novel strategy to control neuropathic pain.

Disclosures: Q. Zeng: None. **M. Addorisio:** None. **M. Gunasekaran:** None. **S. Chavan:** None. **U. Andersson:** None. **K. Tracey:** None. **H. Yang:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.07/DD9

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01 NS097880
NIH Grant R01 NS055976

Title: Peripheral macrophage recruitment to the dorsal root ganglia is critical to pain development after spinal cord injury

Authors: *S. J. CHHAYA[1], J. D. HOULE[1], M. R. DETLOFF[2]
[1]Neurobio. and Anat., [2]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Spinal cord injury (SCI) damages sensory systems and causes chronic, intractable neuropathic pain. Recruitment of macrophages and immune alterations in the dorsal root ganglia (DRG) can modulate nociceptor physiology and afferent sprouting, which are critical processes in SCI pain. This study examines whether macrophage recruitment to the DRG after SCI is

essential to pain development, and if the phenotype and cytokine release profile of macrophages in the DRG can dictate pain development. Adult female Sprague-Dawley rats received unilateral cervical (C5) contusive SCI that causes pain development in 40% of rats. We assessed the immune response to SCI in the C7 and C8 DRGs corresponding to the forepaw dermatome. At 12, 24, 48, 72 and 120 hours post-injury (hpi), CCL2 levels in the DRG were assessed using ELISA and qPCR. Macrophage phenotype markers mRNA and pro-inflammatory cytokine mRNA expression in the DRG were measured via qPCR. Macrophage recruitment into the DRG was assessed with ED1 immunohistochemistry. A cohort of rats received INCB3344, a CCL2 receptor antagonist intravenously for 72hpi after SCI to prevent myeloid cell recruitment. These rats were tested for pain development via von Frey and the mechanical conflict-avoidance paradigms. We observed a rapid, transient spike of CCL2 in the DRG, followed by recruitment of ED1+ cells to the DRG. 50% of rats showed elevated macrophages in the DRG at 120 hpi while the rest maintained near-normal levels. This echoes pain development seen in a subset of SCI rats at 28 dpi. Further, qPCR revealed two distinct clusters of rats—those with elevated pro-inflammatory cytokines in the DRG, or with normal expression. These early differences in cytokine profiles may predict pain development. SCI rats that received INCB3344 upto 72 hpi have fewer macrophages in the DRG at 120 hpi compared to vehicle-treated rats. We are currently assessing whether blockade of macrophage infiltration to the DRG alters SCI-induced pain behaviors. Our data supports the hypothesis that there is a dichotomy in the peripheral immune response to SCI that dictates neuropathic pain development. Future studies will examine the role of macrophage recruitment in causing nociceptor dysfunction as a mechanism contributing to SCI-induced pain.

Disclosures: S.J. Chhaya: None. **J.D. Houle:** None. **M.R. Detloff:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.08/DD10

Topic: D.03. Somatosensation: Pain

Support: Wolfson Experimental Neurology Centre PhD Studentship

Title: *In vivo* imaging reveals nociceptors acquire de novo cold sensitivity to drive cold allodynia in neuropathic pain

Authors: *D. I. MACDONALD, A. P. LUIZ, E. C. EMERY, J. N. WOOD
UCL, London, United Kingdom

Abstract: Innocuous cooling can elicit excruciating pain in patients suffering from peripheral neuropathy. This cold allodynia is recapitulated in mouse models of neuropathic pain which

show hypersensitivity to cooling. While cold sensing in the healthy state is relatively well understood, the cells and molecules that drive cold allodynia remain unclear. Here, we used *in vivo* calcium imaging of peripheral somatosensory neurons to ask which subsets of cells contribute to cold allodynia in neuropathic pain and by what mechanism. In healthy mice, cold-sensing neurons formed a rare population of small-diameter neurons that did not respond to any other stimulus modality. Cold hypersensitivity was elicited in male and female Pirt-GCaMP3 mice by intraplantar injection of the chemotherapeutic oxaliplatin (~3 mg/kg), which triggers cold allodynia within hours in human patients. Imaging of mice the same day as injection revealed oxaliplatin led to a population of large-diameter, mechanically-sensitive neurons acquiring a *de novo* sensitivity to cooling. There was no change in the response sizes or activation thresholds of the basally cold-sensing population. Combined functional and anatomical imaging *in vivo* revealed these neurons did not express *Ntrk2*, which labels low-threshold mechanosensors, but did overlap with *SCN10a*-expressing cells, a classic marker of mechanonociceptors. However, the voltage-gated sodium channel subtype $Na_v1.8$, reported to be critical for cold pain, was dispensable for *de novo* cold sensitivity. Intraplantar injection of 4-aminopyridine (10 mM), a non-selective inhibitor of voltage-gated potassium channels, induced cold responsiveness in previously cold-insensitive neurons within minutes. This points to functional downregulation of voltage-gated potassium channel subtypes expressed by nociceptors as a putative mechanism of *de novo* cold sensitivity in neuropathic pain. Taken together, these data implicate *de novo* cold sensitivity of mechanically-responsive nociceptors as driving cold allodynia induced by oxaliplatin. We are now investigating whether *de novo* cold sensitivity is a feature of cold allodynia resulting from nerve injury and ciguatera in order to determine whether different neuropathic pain conditions share common cellular and molecular mechanisms.

Disclosures: D.I. MacDonald: None. **A.P. Luiz:** None. **E.C. Emery:** None. **J.N. Wood:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.09/DD11

Topic: D.03. Somatosensation: Pain

Support: R01 DE022757/DE/NIDCR NIH HHS/United States
Veterans Affairs San Diego Healthcare System
R01 DE022757/National Institute of Dental and Craniofacial Research/
I01 BX000638/BX/BLRD VA/United States

Title: Mitochondrial perturbations in sensory neurons exposed to fragments of myelin basic protein

Authors: *S. K. HULLUGUNDI[1,2], A. G. REMACLE[3], J. H. SIAMWALA[1], J. SCHILLING[1], A. V. CHERNOV[3], J. DOLKAS[1,2], A. Y. STRONGIN[3], H. PATEL[1,2], V. I. SHUBAYEV[1,2]
[1]Univ. of California San Diego, LA Jolla, CA; [2]VA San Diego Healthcare System,, La Jolla, CA; [3]Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: Myelin basic protein (MBP), a major myelin sheath protein, is an autoantigen. The immunodominant MBP84-104 epitope released from intact MBP is thought to contribute to painful peripheral neuropathy. RNA-seq-based pathways analyses of sciatic nerves injected with MBP84-104 identified mitochondrial dysfunction among the most activated pathways. Thus, we aimed to evaluate the effects of MBP84-104 peptide on the mitochondrial bioenergetics in sensory neurons. Our pull-down and mass spectroscopy studies performed in rat primary dorsal root ganglia (DRG) cultures revealed that the MBP84-104 peptide was capable of binding several ATP-dependent proteins associated with mitochondrial function, including voltage-dependent anion-selective channel 1 (VDAC-1), sodium potassium ATPase and ATP synthase. MBP84-104 did not affect cell viability of DRG cultures, as indicated by a minimal intracellular uptake of calcein dye. Extracellular flux analysis in adult rat DRG cultures at different time points of exposure to the peptide showed that neither ATP-linked respiration nor maximal respiration (both normalized to basal respiration) was significantly altered by the MBP84-104 peptide. However, MBP84-104 reduced the extracellular acidification rate (normalized to the basal levels) of female, compared to male, rat DRG cultures indicating specific alteration in glycolysis. This reduction possibly reflects a switch in neuronal substrate utilization. TEM analysis of DRG cultures treated with MBP84-104 for 24 hours revealed the presence of a high number of small mitochondria in neurons when compared to neurons from control cultures. Overall, it is likely that after their release into microenvironment, the myelin degradation products may affect mitochondrial structure and function in sensory neurons. Our preliminary data also suggests potential sexual dimorphism in this mechanism.

Disclosures: S.K. Hullugundi: None. **A.G. Remacle:** None. **J.H. Siamwala:** None. **J. Schilling:** None. **A.V. Chernov:** None. **J. Dolkas:** None. **A.Y. Strongin:** None. **H. Patel:** None. **V.I. Shubayev:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.10/DD12

Topic: D.03. Somatosensation: Pain

Title: Decreased protein expression of anoctamin-1 contributes to reduce neuropathic pain induced by spinal nerve ligation

Authors: *G. GARCÍA[1], V. A. MARTINEZ-ROJAS[2], E. J. GUTIÉRREZ-LARA[3], J. MURBARTIAN[4]
[1]Cinvestav Sede Sur, Mexico DF, Mexico; [2]Cinvestav Sede Sur, Mexico City, Mexico; [3]Pharmacol., CINVESTAV, Distrito Federal, Mexico; [4]Cinvestav, Sede Sur, Mexico, DF, Mexico

Abstract: Anoctamin-1 belongs to the family of calcium–activated chloride channels and is expressed in dorsal root ganglion (DRG) neurons. The activation of anoctamin-1 leads the development of the neuronal excitability observed in neuropathic pain. The aim of this study was to determine the participation of anoctamin-1 in two models of neuropathic pain in rats: L5/L6 spinal nerve ligation (SNL) and L5 spinal nerve transection (SNT).
We determined the protein expression of Anoctamin-1, as well as neuronal injury marker ATF-3 and apoptosis marker caspase-3 in injured L5 and in uninjured L4 DRG at 1, 3, 7, 14 and 21 days after SNL and SNT. SNL up-regulated anoctamin-1 protein expression in injured L5 and uninjured L4 DRG, but not after SNT. Whereas that ATF-3 and caspase-3 increased their expression only in injured L5 in SNL and SNT, but not in uninjured L4 DRG. In addition, repeated (3 times every 24 h) intrathecal (i.t.) injection of the anoctamin-1 blockers, $T16A_{inh\text{-}A01}$ (0.1-1 µg) or MONNA (1-10 µg), but not vehicle (15% DMSO) reverted tactile allodynia induced by SNL in a dose-dependent manner. In contrast, $T16A_{inh\text{-}A01}$ or MONNA modestly reverted tactile allodynia induced by SNT. Repeated intrathecal injection of $T16A_{inh\text{-}A01}$ or MONNA also reduced SNT-induced up-regulation of ATF-3 in injured L5 DRG but it did not have effect on SNT-induced up-regulation of caspase-3 expression in L5 DRG. Likewise, gabapentin (100 µg) diminished SNL-induced up-regulation of anoctamin-1, ATF-3 and caspase-3 expression in injured L5 DRG.
These data suggest that spinal anoctamin-1 in injured and uninjured DRG participates in the maintenance of neuropathic pain in rats. Our data also indicate that expression of anoctamin-1 in DRG is differentially regulated depending on the neuropathic pain model.

Disclosures: G. García: None. **V.A. Martinez-Rojas:** None. **E.J. Gutiérrez-Lara:** None. **J. Murbartian:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.11/DD13

Topic: D.03. Somatosensation: Pain

Support: Washington University Pain Center
Washington University Nutrition Obesity Research Center
NIH Grant NS069898

NIH Grant CA171927
NIH Grant HL125805
NIH Grant NS42595

Title: Macrophage angiotensin II type-2 receptor triggers neuropathic pain

Authors: *A. J. SHEPHERD[1], A. D. MICKLE[1], J. P. GOLDEN[1], M. R. MACK[1], A. D. DE KLOET[2], V. K. SAMINENI[1], B. S. KIM[1], E. G. KRAUSE[3], R. W. GEREAU, IV[1], D. P. MOHAPATRA[1]
[1]Dept. of Anesthesiol., Washington University, Sch. of Med., Saint Louis, MO; [2]Physiol. and Functional Genomics, Univ. of Florida, Col. of Med., Gainesville, FL; [3]Pharmacodynamics, Univ. of Florida, Gainesville, FL

Abstract: Peripheral nerve damage initiates a complex series of structural and cellular processes that culminate in chronic neuropathic pain. The recent success of a type 2 angiotensin II (Ang II) receptor (AT2R) antagonist in a phase II clinical trial suggests angiotensin signaling is involved in neuropathic pain. However, transcriptome analysis indicates a lack of AT2R gene expression in human and rodent sensory ganglia, raising questions regarding the tissue/cell target underlying the analgesic effect of AT2R antagonism. We show that selective antagonism of AT2R attenuates neuropathic, but not inflammatory mechanical and cold pain hypersensitivity behaviors in mice. AT2R-expressing macrophages constitute the predominant immune cells that infiltrate the site of nerve injury. Interestingly, neuropathic mechanical and cold pain hypersensitivity can be attenuated by chemogenetic depletion of peripheral macrophages and AT2R-null hematopoietic cell transplantation. Our study identifies AT2R on peripheral macrophages as a critical trigger for pain sensitization at the site of nerve injury, and therefore proposes a novel, translatable peripheral mechanism underlying chronic neuropathic pain.

Disclosures: A.J. Shepherd: None. **A.D. Mickle:** None. **J.P. Golden:** None. **M.R. Mack:** None. **A.D. de Kloet:** None. **V.K. Samineni:** None. **B.S. Kim:** None. **E.G. Krause:** None. **R.W. Gereau:** None. **D.P. Mohapatra:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.12/DD14

Topic: D.03. Somatosensation: Pain

Support: The Peggy and Avinash Ahuja Foundation and the Helen Buchanan and Stanley Joseph Seeger Endowment at The University of Texas MD Anderson Cancer Center.

Title: Analgesic and preventive effects of free radical scavengers in chemotherapy-induced neuropathic pain in rats

Authors: *H. KIM, S. ABDI
Dept. of Pain Med., MD Anderson Cancer Ctr., Houston, TX

Abstract: Advances in the treatment of cancer using various types of chemotherapy agents have led to improvement in the survival rate of cancer patients. Unfortunately, pain associated with the chemotherapy including taxanes, vinca alkaloids, and platinum complexes is a dose-limiting adverse effect which affects the quality of life of the survivals. The purpose of study was to determine the analgesic and preventive effects of Tempol, a free radical scavenger, on paclitaxel (PAC)-induced neuropathic pain in rats. PAC-induced neuropathic pain was produced by interaperitoneal injections of PAC (2 mg/kg on days 0, 2, 4, 6) in adult male Sprague-Dawley rats. The pain behavioral tests as well as western blotting and live cell imaging of the L1-6 dorsal root ganglia (DRGs) were performed. Tempol was intraperitoneally injected or infused beginning on day 0, 6, or 20. For the analgesic effect, the single injection and infusion of Tempol reduced pain behaviors on day 20. PAC increased the levels of inflammatory cytokines and mitochondrial superoxide anion in the DRGs tissues and culture. However, Tempol decreased PAC-induced cytokines and superoxide anion. For the prevention, the infusion of Tempol beginning on day 0 for 1 week did not affect the development of pain behavior. In contrast, the infusion of Tempol beginning on day 6 for 1 week completely prevented further development of pain behavior. We conclude that Tempol alleviates and prevents chemotherapy-induced neuropathic pain in rats by reducing the levels of inflammatory cytokines and free radicals in the DRGs.

Disclosures: H. Kim: None. **S. Abdi:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.13/DD15

Topic: D.03. Somatosensation: Pain

Support: The project is funded by the Interdisciplinary Center for Clinical Research (IZKF, N-353) of the University of Wuerzburg

Title: Extended use of diagnostic skin punch biopsies of SFN patients to multiply limited material for new *in vitro* tools to investigate small fiber pathology

Authors: *F. KARL[1], T. MALZACHER[1], K. LUISA[1], S. NADINE[1], C. SOMMER[1], F. GROEBER-BECKER[2], N. ÜÇEYLER[1]

[1]Dept. of Neurol., Univ. of Wuerzburg, Wuerzburg, Germany; [2]Translational Ctr. Wuerzburg 'Regenerative Therapies in Oncology and Musculoskeletal Diseases', Wuerzburg Br. of the Fraunhofer-Institute Interfacial Engin. and Biotechnology, IGB, Wuerzburg, Germany

Abstract: Background and Objective: Small fiber neuropathy (SFN) is characterized by acral burning pain and dysesthesias. SFN primarily affects thinly myelinated A-delta and unmyelinated C fibers responsible for pain and thermal perception. The underlying mechanisms of SFN are unknown and research is hampered by the limited availability of biomaterial restricted to few mm² of diagnostic skin punch biopsies taken for intraepidermal nerve fiber density (IENFD) assessment. Our aim was to determine innervation patterns on skin biopsies of SFN patients, to establish primary fibroblast and keratinocyte cell cultures from 6-mm skin biopsies, and to generate patient-derived threedimensional (3D)-full thickness skin models (FTM) as an in vitro model to investigate small fiber pathology.
Methods: So far we recruited 56 SFN patients and healthy controls. Skin punch biopsies were taken from the lateral lower leg and the upper thigh. The IENFD was determined on one half of the biopsy by immunohistochemistry of protein gene product 9.5 and innervation patterns were determined compared to controls. The second part of the biopsy was used to isolate human dermal fibroblasts (HDF) and human epidermal keratinocytes (HEK) for primary cell culture. Additionally, HEK and HDF from adult healthy controls were used to establish a compressed FTM containing a collagen type I hydrogel. The histological structure of FTM was assessed using immunohistochemistry with hematoxylin-eosin.
Results: When applying the normative values of our laboratory obtained from n=180 healthy subjects, four patterns of skin innervation were found in SFN patients: distally reduced IENFD (women: 26%, men: 23%; control women 11%, control men 19%), proximally reduced IENFD (women: 3%, men: 9%; controls women: 3%, controls men:none), generally reduced IENFD (women: 21%, men: 45%; controls women: 3%, controls men: none), and normal IENFD (women: 50%, men 23%, control women 82%, control men 81%). Thus, 37% of SFN patients had normal skin innervation while reporting typical symptoms. We established primary cell cultures of HDF and HKF from 6-mm skin punch biopsies, and also succeeded in generating first FTM displaying regular human skin histology as an in vitro tool for pathophysiology research.
Conclusions: There is a relevant subpopulation of SFN patients that may be missed by current diagnostics due to normal skin innervation, which does not exclude the diagnosis. Thus, besides nociceptor quantity, potential local factors influencing nociceptor sensitivity need to be considered, which can be studied using primary cell cultures and FTM in future studies.

Disclosures: F. Karl: None. **T. Malzacher:** None. **K. Luisa:** None. **S. Nadine:** None. **C. Sommer:** None. **F. Groeber-Becker:** None. **N. Üçeyler:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.14/DD16

Topic: D.03. Somatosensation: Pain

Support: This project was funded by the Center for Interdisciplinary Clinical Research (Interdisziplinäres Zentrum für klinische Forschung, IZKF; N-260), University of Wuerzburg, Germany.

Title: Effect of neuronal globotriaosylceramide deposits on pain and sensory impairment in Fabry disease

Authors: *L. HOFMANN[1], D. HOSE[1], S. D. DIB-HAJJ[3], S. WAXMAN[3], C. SOMMER[1], E. WISCHMEYER[2], N. ÜÇEYLER[1]
[1]Dept. of Neurol., [2]Inst. of Physiol., Univ. of Wuerzburg, Wuerzburg, Germany; [3]Dept Neurol, Yale Sch. of Med. and VAMC, West Haven, CT

Abstract: Background and Objective: Fabry disease (FD) is an X-linked, progressive and life-threatening inherited lysosomal storage disorder with intracellular accumulation of globotriaosylcermaide (Gb3) due to α-galactosidase A (α-Gal A) deficiency. Starting in early childhood, Fabry patients characteristically suffer from episodic acral burning pain particularly triggered by heat and fever that substantially limits health related quality of life. We aimed to elucidate the mechanism linking neuronal Gb3 deposits with pain and sensory impairment, using the α-galactosidase A knockout (GLA KO) mouse as a model for FD. Additionally, we investigated the effect and potential reversibility of Gb3 depositions on pain associated ion channel function in an in vitro model of FD.
Methods: We investigated the localization of Gb3 in dorsal root ganglion (DRG) neurons of young (3 months) and old (12-24 months) GLA KO mice compared to wildtype (WT) littermates. Patch-clamp analysis was used for characterization of transient receptor potential vanilloid 1 (TRPV1), hyperpolarization-activated (I_h), and voltage-gated-sodium currents in cultured DRG neurons. We assessed pain associated behavior after intraplantar injection of capsaicin, chronic constriction nerve injury (CCI) of the sciatic nerve, and intraplantar injection of complete Freund`s adjuvant (CFA) as pain models. Finally, we investigated the effect of Gb3 accumulation on neuronal ion channel function in human embryonic kidney 293 (HEK) cells expressing voltage-gated sodium channel 1.7 ($Na_v1.7$), induced by α-Gal A silencing.
Results: Gb3 was increased in DRG neurons of old GLA KO mice compared to WT littermates and young mice. While electrophysiological characteristics of TRPV1 currents did not differ between genotypes, old GLA KO mice displayed increased and sustained heat hypersensitivity compared to old WT mice ($p<0.05$) after intraplantar capsaicin injection. In contrast, I_h- and

sodium-currents were notably reduced ($p<0.001$ each) in old GLA KO mice compared to old WT mice. Accordingly, old GLA KO mice did not develop heat or mechanical hypersensitivity after CCI and intraplantar injection of CFA ($p<0.001$ each). Finally, HEK cells in which α-Gal A was silenced by small hairpin RNA displayed an increase in Gb3 deposition and a subsequent reduction of $Na_v1.7$ currents ($p<0.01$) compared to control cells. Both effects were reversed by agalsidase-α incubation 24 hours prior patch-clamp analysis ($p<0.05$).
Conclusions: Our study provides first evidence for a direct effect of Gb3 on neuronal ion channel function as a potential contributor to pain and sensory disturbance in FD.

Disclosures: L. Hofmann: None. **D. Hose:** None. **S.D. Dib-Hajj:** None. **S. Waxman:** None. **C. Sommer:** None. **E. Wischmeyer:** None. **N. Üçeyler:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.15/DD17

Topic: D.03. Somatosensation: Pain

Support: IRP, NIDA, NIH

Title: Epigenetic modification by sigma-1 receptor at the dorsal root ganglion in neuropathic pain

Authors: *N. GOGUADZE, H.-E. WU, T.-P. SU
Cell. Pathobiology Section, NIDA, IRP, NIH, Baltimore, MD

Abstract: Chronic neuropathic pain alters nociceptive signal processing that causes suffering and reduces quality of life. The ER chaperone sigma-1 receptor (Sig-1R) was demonstrated to play a role in neuropathic pain and is known to exist in the dorsal root ganglia (DRG), notably, at the nuclear envelope. However, the molecular mechanisms whereby Sig-1Rs modulate neuropathic pain at the DRG are largely unknown. This study was undertaken to examine the role of Sig-1R on the DRG on the behavioral and molecular level.
In naïve rats, direct DRG injection (4^{th} and 5^{th} lumbar DRG) of the Sig-1R agonist (+)-pentazocine produced a hypersensitivity to threshold mechanical stimulation, as well as a trending hypersensitivity to noxious mechanical, brush, or cold stimulation. In “spared nerve injury” rats, the Sig-1R antagonist BD1047 caused a reduction in neuropathic hypersensitivity. At the molecular level, we noticed that the inhibition of histone methyltransferase at the DRG was recently shown to attenuate the neuropathic pain by correcting the dysfunctional potassium channels. Inasmuch as Sig-1Rs exist at the nuclear envelope, we hypothesized that Sig-1Rs may participate in the transcriptional regulation of epigenetic enzymes related to neuropathic pain. Therefore, we examined enzymes which affect the histone methylation/acetylation as well as

their respective products in DRGs from wild type and Sig-1R knockout mice. Immunoblottings from Sig-1R knockout DRGs, when compared to wild type DRG, showed a decrease in the level of the enhancer of zeste homolog 2 methyltransferase (EZH2) and euchromatic histone-lysine N-methyltransferase-2 (G9a). However, the level of the mixed-lineage leukemia 1 methyltransferase (MLL1) was increased in the Sig-1R knockout DRG. Correspondingly, the resultant level of the product for EZH2 and G9a, i.e., H3K27me3 and H3K9me2 respectively, was reduced whereas the H3K4me3 for MLL1 was increased. Our results suggest that the Sig-1R participates in the genesis of neuropathic pain through the epigenetic modification of histone in the DRG.

Disclosures: N. Goguadze: None. **H. Wu:** None. **T. Su:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.16/DD18

Topic: D.03. Somatosensation: Pain

Support: NIH Grant 5F32NS100404
NIH Grant 1R01NS101704
NIH Grant 1R35NS105076

Title: Functional and transcriptional changes in primary somatosensory neurons after peripheral nerve injury

Authors: *I. TOCHITSKY[1], W. RENTHAL[2], D. YARMOLINSKY[5], I. M.-C. CHIU[3], Y.-C. CHENG[5], B. SINGH[6], M. E. GREENBERG[4], C. J. WOOLF[7]
[1]Neurobio., Boston Children's Hosp. and Harvard Med. Sch., Boston, MA; [2]Neurobio., [3]Microbiology and Immunobiology, [4]Dept. of Neurobio., Harvard Med. Sch., Boston, MA; [5]Neurobio., Boston Children's Hosp., Boston, MA; [6]FM Kirby Neurobio. center, Boston Children's Hosp. Harvard Med. Sch., Boston, MA; [7]Neurobio., Children's Hosp. Boston, Boston, MA

Abstract: Objective/Specific Aims: Identify functional and transcriptional changes in primary somatosensory neurons after peripheral nerve injury and determine their contribution to neuropathic pain
Background: Neuropathic pain is a common disorder typically caused by disease of or damage to the peripheral nervous system. Spontaneous pain is a major feature of neuropathic pain disorders and is thought to be generated by the ectopic activity of peripheral somatosensory neurons. Unfortunately, it is not known which subtypes of peripheral sensory neurons become spontaneously active after nerve injury or what changes in gene expression cause their

hyperexcitability. Here, we present functional and transcriptional data exploring the changes that take place in injured somatosensory neurons and contribute to their hyperexcitability. Results and significance: Sciatic nerve injury, an animal model of neuropathic pain, produces thermal and mechanical hyperalgesia, and mechanical allodynia, which are also present in patients with neuropathic pain. At various time points after sciatic nerve injury, we dissected and cultured lumbar L3-L5 dorsal root ganglia (DRG) neurons in vitro and then performed functional and transcriptional analyses on these cultured neurons. We observed a higher incidence of spontaneous activity and higher excitability in ipsilateral injured DRG neurons as compared to naive control DRG neurons using both patch clamp electrophysiology and calcium imaging. We also observed a lower density of voltage gated potassium currents in ipsilateral DRG neurons, consistent with their hyperexcitability. Finally, we performed a single cell transcriptional analysis on injured vs naive DRG neurons and found a number of differences in gene expression associated with injury and consistent with injury-induced hyperexcitability. We believe that a combined functional and transcriptional analysis may help identify changes that take place in defined subpopulations of somatosensory neurons in neuropathic pain and potentially identify new drug targets for the treatment thereof.

Disclosures: I. Tochitsky: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Carica Health. **W. Renthal:** None. **D. Yarmolinsky:** None. **I.M. Chiu:** None. **Y. Cheng:** None. **B. Singh:** None. **M.E. Greenberg:** None. **C.J. Woolf:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.17/EE1

Topic: D.03. Somatosensation: Pain

Support: National Natural Sciences Foundation of China-Youth science fund/81701112

Title: Histone demethylase LSD1 in peripheral sensory neurons regulates neuropathic pain in rats with chronic compression of dorsal root ganglion

Authors: *L. LIANG[1], S. WANG[1], X. ZHU[2], Y. CHEN[1], Y. WANG[3], F. HUO[3], S. JIA[2], S. LU[3]
[1]Xi'An Jiaotong Univ. Hlth. Sci. Ctr., Shaanxi, China; [2]Anesthesiol., Yantai Affiliated Hosp. of Binzhou Med. Univ., Yantai, China; [3]Key Lab. of Envrn. and Genes Related to Dis., Beijing, China

Abstract: Neuropathic pain is one of the most refractory and painful diseases in clinic and is lack of effective drug therapy due to unclear mechanisms. Histone methylation is one of major

epigenetic mechanism for gene expression and has been reported involved in the nerve injury induced neuropathic pain. Lysine-specific demethylase 1 (LSD1) is the first identified subfamily of histone Nε-methylated lysine residue demethylases. A previous RNA-seq data have analyzed the whole genome gene expression from sham and spinal nerve ligated DRGs and found the increased expression of LSD1 mRNA in injuried DRG. However, it is not clear if LSD1 contributes to neuropathic pain genesis. In this study, using two rat neuropathic pain models of spinal nerve ligation or chronic compression of dorsal root ganglion (CCD), we confirmed the increased LSD1 mRNA and protein levels in injured DRGs by qPCR or western blot methods. LSD1 inhibitor SP2509 or LSD1 siRNA relieved bilateral pain hypersensitivities to mechanical, thermal and cold stimuli. Moreover, LSD1 siRNA reversed the increased LSD1 and the decrease of its catalytic site histone 3 lysine 4 dimethylation (H3K4me2) expression induced by CCD. These data suggests that LSD1 may be a new potential target for neuropathic pain intervention.

Disclosures: L. Liang: None. **S. Wang:** None. **X. Zhu:** None. **Y. Chen:** None. **Y. Wang:** None. **F. Huo:** None. **S. Jia:** None. **S. Lu:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.18/EE2

Topic: D.03. Somatosensation: Pain

Support: R01 AA025967
R21 AA023051
T32-AA014127
P50 AA022534

Title: Neuropathic pain susceptibility in prenatal alcohol exposed (PAE) females is mediated by the proinflammatory actions of lymphocyte function-associated antigen (LFA)-1 on immune and glial cells

Authors: *S. NOOR[1], J. SANCHEZ[1], Z. PERVIN[1,2], J. SANCHEZ[1], M. S. SUN[1], L. EPLER[1], S. DAVIES[1], D. SAVAGE[1], N. MELLIOS[1], L. JANTZIE[1,3], E. MILLIGAN[1]
[1]Dept. of Neurosciences, [2]Dept. of Chem. and Biol. Engin., [3]Dept. of Pediatrics, Univ. of New Mexico, Albuquerque, NM

Abstract: Previous work demonstrates that PAE male rat offspring with peripheral nerve injury augments spinal and peripheral immune cell responses and elevates pro-inflammatory cytokine levels that underlie heightened allodynia (non-painful stimuli perceived as painful) in PAE rats. Furthermore, upregulation of adhesion molecules such as LFA-1, occur concurrently with PAE and allodynia. In the current study, female PAE rats were examined to determine whether a

similar pattern of allodynia is observed following sciatic neuropathy induced by either standard (4 suture) chronic constriction injury (CCI) or minor nerve injury (a *single* suture CCI) as seen in males. In addition, the LFA-1 antagonist, BIRT377 was used to explore the critical actions of peripheral immune cells/factors underlying peripheral neuropathy in these rats. Data demonstrate that females display neuropathic susceptibility following standard or minor nerve injury, which could be reversed by *intravenous* but not *intrathecal* (spinal) injection of BIRT377. In contrast, BIRT377 suppressed neuropathy in males via both routes of administration. These data suggest blocking the actions of immune cells factors by suppressing LFA-1 actions in the spinal cord is not sufficient to reverse allodynia in females, suggesting sex-related differences exist between spinal immune phenotypes that contribute to neuropathic pain. The sciatic nerve, dorsal root ganglia and spinal cord were collected from these females to investigate the underlying PAE-related immune mechanisms and the effects of BIRT377. Real time PCR and protein (via multiplex) cytokine analysis demonstrate that the pro-inflammatory cytokines, tumor necrosis factor (TNF) and interleukin (IL)-1β are greater in PAE rats with allodynia than the control rats. A CCI injury-induced compensatory increase of the anti-inflammatory cytokine, IL-10 occurs at the sciatic nerve in non-PAE rats, while PAE females display blunted IL-10 responses. BIRT377 treatment reduces TNF and IL-1β and rescues normal IL-10 expression in neuropathic PAE rats. Moreover, augmented glial activation (GFAP mRNA levels) occurs in PAE females with neuropathy compared to the control animals, suggesting astrocyte activation may contribute to neuropathic susceptibility in PAE females. BIRT377 treatment reduced astrocyte activation in neuropathic PAE rats. These data suggest that exaggerated peripheral immune cell and glial actions lead to the development of neuropathic pain susceptibility in PAE females that is reduced by BIRT377 by promoting an anti-inflammatory environment.

Disclosures: S. Noor: None. **J. Sanchez:** None. **Z. Pervin:** None. **J. Sanchez:** None. **M.S. Sun:** None. **L. Epler:** None. **S. Davies:** None. **D. Savage:** None. **N. Mellios:** None. **L. Jantzie:** None. **E. Milligan:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.19/EE3

Topic: D.03. Somatosensation: Pain

Support: KHIDI Grant HI15C0007
KIOM Grant K18181

Title: The analgesic efficacy of low frequency stimulation in docetaxel-induced neuropathic pain decreases ultrasound vocalizations in mice

Authors: *S.-Y. KANG[1], Y. RYU[1], S.-Y. SEO[1], O. KWON[1], K.-H. CHOI[1], S. CHO[1], H. YOO[2], J. LEE[3]
[1]Korea Inst. of Oriental Med., Daejeon, Korea, Republic of; [2]East West Cancer Center, Dunsan Korean Med. Hosp. of Daejeon Univ., Daejeon, Kosovo, Republic of; [3]Dept. of surgery, Chungnam Natl. Univ. Hosp., Daejeon, Korea, Republic of

Abstract: Objective. Docetaxel, a chemotherapeutic agent used to treat breast cancer, produces a robust painful neuropathy that is aggravated by mechanical and thermal stimuli. This study was undertaken to investigate the analgesic effects of low frequency stimulation on docetaxel-induced neuropathic pain in mice and to identify associated changes in ultrasound vocalizations. **Methods.** Peripheral neuropathy was induced with intraperitoneally injected docetaxel (5mg/kg) on 3 times every 2 days in male ICR mice. Low frequency wrist stimulation (Care band, 16 Hz) was administered and pain behavior signs were evaluated by von Frey filaments and thermal stimulation on the hind paw. Ultrasound vocalizations were measured using ultrasound microphones (frequency range: 10-200 kHz, Avisoft Bioacoustics), after low frequency stimulation. **Results.** After mice developed docetaxel-induced neuropathic pain behavior, a single low frequency stimulation temporarily attenuated mechanical allodynia and thermal hyperalgesia. In formalin and NMDA test, pain-induced mice showed increases in 10-30 kHz ultrasound vocalizations, but not in 30-50 and 50-80 kHz vocalizations. Treatment with docetaxel for 3 times every 2 days selectively increased 10-30 kHz ultrasound vocalizations, whereas low frequency stimulation caused a meaningful decrease. **Conclusions.** These results suggest that low frequency stimulation can be a potential strategy for the management of chemotherapy-induced neuropathy. We showed the ability of low frequency stimulation to attenuate pain in a mouse model of chemotherapy-induced neuropathy. This approach could potentially provide a new method to treat peripheral neuropathic pain in cancer patients.

Disclosures: S. Kang: None. **Y. Ryu:** None. **S. Seo:** None. **O. Kwon:** None. **K. Choi:** None. **S. Cho:** None. **H. Yoo:** None. **J. Lee:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.20/EE4

Topic: D.03. Somatosensation: Pain

Title: A conditioning lesion induces an arachidonic acid-containing phosphatidylcholine level increase and lysophosphatidic acid precursors level decrease in the dorsal root ganglion of mice

Authors: *Y. MIHARA[1], T. OMURA[2]
[1]Orthopaedic Surgey, Hamamatsu Univ. Sch. of Med., Hamamatsu/Shizuoka, Japan; [2]Hamamatsu Univ. Sch. of Med., Hamamatsu, Shizuoka, Japan

Abstract: [Introduction] Pre-conditioning peripheral nervous system neurons by a peripheral axonal injury primes them through massive transcriptional changes to regenerate more vigorously. Conditioning lesion also triggers cellular and molecular changes in the dorsal root ganglion (DRG) and promotes intrinsic growth capacity for nerve regeneration in the DRG neurons. However, little is known about how lipids are regulated in the DRG after conditioning lesion. Previously we reported lipid investigations of several nervous systems using matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS). In this study, lipids changes of DRG after conditioning lesion were analyzed using MALDI-IMS. [Experimental procedure] 8-week-old C57BL/6JJmsSlc male mice were used for this study. Sciatic nerve transection (SNT) was performed by transection of the left sciatic nerve at mid-thigh level under anesthesia. Five days after SNT, 3 mice were sacrificed and L4-6 DRG were extracted for analysis. The same number of naive mice was used as controls. These DRGs were flesh frozen and were cut at -20℃ using a cryostat, then placed alternately onto glass slides coated with indium-tin-oxide. IMS analyses were performed using a MALDI time-of-flight (TOF)/TOF-type instrument (Solarix XR). Regions of interests (ROIs) in DRG were determined by selecting 20 points randomly. [Results] We found that arachidonic acid-containing phosphatidylcholine (AA-PC), [PC(16:0/20:4)+K]+ , increased significantly in the DRG after sciatic nerve transection (SNT). Moreover, [PC(16:0/18:1)+K]+, [PC(18:0/18:1)+ K]+ and [phosphatidic acid (PA)(36:2)+K]+ decreased significantly in the DRG after SNT. [Discussion] According to our previous research, the increase of [PC(16:0/20:4)+K]+ is associated with neuropathic pain. The decrease of [PC(16:0/18:1)+K]+, [PC(18:0/18:1)+ K]+ and [PA(36:2)+K]+ might be induced by production of lysophosphatidic acid (LPA), a initiator of neuropathic pain. There are 2 major pathways for synthesis of LPA. One is from lysophosphatidylcholine (LPC) by autaxin (ATX) enzymes. Another is from PA by phospholipase A2 (PLA2) enzymes. Reduction of [PC(16:0/18:1)+K]+ and [PC(18:0/18:1)+ K]+ might be as a consumption by the former pathway to produce LPA. [PA(36:2)+K]+ was also consumed by the latter pathway. [Conclusion] These results suggest that mechanisms of conditioning lesion might be associated with neuropathic pain. Suitable nerve stimulation must be benefit for nerve regeneration, though neuropathic pain is the excessive stimulation of nerve.

Disclosures: Y. Mihara: None. **T. Omura:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.21/EE5

Topic: D.03. Somatosensation: Pain

Support: NIH-AR047410

Title: The immunoreactive expression pattern of neun as a neuronal-nuclei qualifier for high-throughput data analysis in rat dorsal root ganglion: 2-day adjuvant-induced arthritis

Authors: *M. B. ANDERSON, K. E. MILLER
Oklahoma State Univ., Tulsa, OK

Abstract: Automated high-throughput data analysis in neuronal tissue is currently an uncommon practice. This is typically due to strict software parameters required to identify neurons within tissue sections that have morphological differences and immunohistochemical labeling variability. Also, available fluorescent markers to identify cellular landmarks must be relatively consistent in their intensity between control and experimental conditions to identify consistent populations of neurons. In dorsal root ganglion (DRG), the requirement of a proofing-system is critical in the automatic and successful selection of neurons due to the presence of satellite/glial cells. To overcome these obstacles, we utilized the nuclear marker DAPI (4' 6-Diamidino-2-Phenylindole, Dihydrochloride) and NeuN immunoreactivity (ir) to automatically identify and select neuronal nuclei from a heterogeneous cell population in frozen tissue sections. NeuN has been shown to be expressed in nuclear ($NeuN_N$), cytoplasmic ($NeuN_C$), nuclear/cytoplasmic ($NeuN_{NC}$), or NeuN negative neural cell populations. In addition, peripheral nerve resectioning has shown a near-complete loss of NeuN-ir in facial motoneurons. Due to the reported differences of NeuN-ir, it is important to carefully evaluate its expression as a neural selective marker in specific control and experimental conditions. The focus of this study was to evaluate the immunoreactive expression and use of NeuN in DRG neurons as a neuronal-nuclei qualifier, in conjunction with DAPI, for the automatic identification of neurons in the high-throughput data analysis of frozen tissue sections from rat DRG during adjuvant-induced arthritis (AIA). To further understand any potential subcellular changes of NeuN, we examined whole cell, cytoplasmic, and nuclear expression of NeuN between experimental conditions with immunohistochemistry and western blots. Glutaminase (GLS), the enzyme for neurotransmitter glutamate synthesis, also was evaluated during AIA. AIA was induced by injection of complete Freund's adjuvant into the right hindpaw of anesthetized rats. A reliable and robust script for ImageJ was written that produces neuronal-nuclei seed images based on the presence of DAPI within the boundary of NeuN-ir. This script was designed to be flexible enough to overcome observed variability of NeuN-ir and was successful in its ability to equally measure both control and AIA neuronal cell populations. High-throughput data analysis was achieved using these seed images and establishes a novel method of high-throughput evaluation of frozen tissue sections from rat DRG neurons during AIA.

Disclosures: M.B. Anderson: None. **K.E. Miller:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.22/EE6

Topic: D.03. Somatosensation: Pain

Support: NIAAA #AA025967-01
NIAAA #AA022534-01
NIAAA #AA023051
NIDA #DA018156-10
STC.UNM 2014 Gap Funding Award

Title: BIRT377, an inhibitor of lymphocyte function-associated antigen 1, suppresses allodynia in males and females through different immune signaling cytokines

Authors: *M. S. SUN[1], S. NOOR[1], A. G. VANDERWALL[1,2], M. A. HAVARD[2], J. E. SANCHEZ[1], N. W. HARRIS[1], M. V. NYSUS[3], J. P. NORENBERG[3], E. D. MILLIGAN[1]
[1]Neurosciences, [2]Anesthesiol. and Critical Care, [3]Radiopharmaceutical Sci., Univ. of New Mexico, Albuquerque, NM

Abstract: Recent evidence suggests that peripheral neuropathic pain relies on immune cell phenotype and function that may be sexually dimorphic. BIRT377 is a small molecule inhibitor of lymphocyte function-associated antigen 1 (LFA-1), a β_2 integrin adhesion molecule expressed on leukocytes such as T cells and monocytes, and is important for migration of these cells into areas of tissue damage. Allodynia (pathological sensitivity to light touch) is observed in rodent models of peripheral neuropathy such as the Chronic Constriction Injury (CCI) of the sciatic nerve. During neuropathic pain, T cell actions are observed to play a greater role in female rodents than in males. Recently, we reported that blocking LFA-1 actions robustly reverses allodynia in male and female mice with CCI, with its actions occurring specifically on female-derived but not male-derived T cells (SfN Poster, 2017, Sun et al.). Therefore, we hypothesized that the sexually dimorphic pain-suppressive actions of BIRT377 occurs by altering discrete proinflammatory signaling molecules (cytokines and chemokines) in anatomical regions of the pain pathway (lumbar spinal cord (LSC), dorsal root ganglia (DRG), sciatic nerve (SCN)). Behavioral hindpaw assessment (von Frey fiber test for light touch threshold responses) of male and female C57BL/6 mice (10-12 wks; N=6/gp) prior to and after sham or CCI (sciatic loose ligation using three 5-0 chromic gut sutures) surgery was performed. On Day 10 after surgery, mice were injected with BIRT377 (intravenous; i.v., tail vein; 2.5 µg in 50µL) or vehicle and assessed daily to Day 3 after injection. mRNA levels were assessed for pro- and anti-inflammatory cytokines (C-C Chemokine Ligand 2 (CCL2), Interleukin-1β (IL-1β), Tumor Necrosis Factor (TNF), IL-10, IL-17A), T_{Reg} cell transcription factor (Forkhead Box P3

(FoxP3)), and the glial activation markers (Glial Fibrillary Acidic Protein (GFAP): astrocytes; Transmembrane Protein 119 (TMEM119): microglia). Differences in various cytokines between male and female mRNA levels following CCI, and separately as a result of BIRT377, were observed in SCN, DRG, and LSC. Specifically, in female SCN, i.v. BIRT377 increased IL-10 mRNA. Sexually distinct decreases of pro-inflammatory CCL2, IL-1β, and TNF mRNA cytokines were seen following BIRT377 treatment. Additionally, decreases in pro-inflammatory cytokine, IL-17A, and increases in anti-inflammatory FoxP3 were seen in female tissues only. GFAP mRNA levels were decreased while TMEM119 remained unaffected by BIRT377. Thus, BIRT377 controls neuropathic pain in both males and females but by affecting different immune and glial cell actions.

Disclosures: M.S. Sun: None. **S. Noor:** None. **A.G. Vanderwall:** None. **M.A. Havard:** None. **J.E. Sanchez:** None. **N.W. Harris:** None. **M.V. Nysus:** None. **J.P. Norenberg:** None. **E.D. Milligan:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.23/EE7

Topic: D.03. Somatosensation: Pain

Support: SBRC Foundation Grant

Title: Over-expression of secreted amyloid precursor protein alpha ameliorates pathological hallmarks of type 1 diabetes

Authors: *G. L. ODERO[1], B. D. AULSTON[2,3], D. R. SMITH[2], G. W. GLAZNER[2,3]
[1]Pharmacol. & Therapeut., [2]Div. of Neurodegenerative Disorders, Albrechtsen Res. Ctr., Winnipeg, MB, Canada; [3]Pharmacol. & Therapeut., Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Secreted amyloid precursor protein alpha (sAPPa) has been shown to confer beneficial properties in central nervous system neurons such as increasing neurite outgrowth, enhancing long-term potentiation and acting in a neuroprotective capacity. However, relatively little is known about the function of sAPPa in the peripheral nervous system, specifically, in the context of diabetes. To study its function, we used transgenic mice that over-expressed sAPPa. Expression of the transgene was detected in whole DRG and sciatic nerve as determined by reverse transcript-polymerase chain reaction (RT-PCR). Immunohistochemistry (IHC) in whole dorsal root ganglia (DRG) detected increased expression of APP protein most dramatically in the satellite glial cells. IHC also indicated increased expression of APP protein in sciatic nerve, presumably in Schwann cells. In this study, wild type and transgenic sAPPa over-expressing mice were rendered type 1 diabetic by injection of streptozotocin. After 4 months of uncontrolled

diabetes, thermal testing revealed retention of thermal sensation in the transgenic sAPPa mice relative to their wild type controls. Furthermore, histological quantitation of intra-epidermal nerve fibers showed a greater density of nerve fibers in the transgenic sAPPa mice relative to their controls. We also report that demyelination of nerve fibers associated with type 1 diabetes was decreased in the diabetic transgenic sAPPa mice relative to their diabetic controls. Hematoxylin and eosin staining indicated no differences in neuronal morphology or distribution of neuronal cell sizes between the wild type and transgnic mice, nor did it indicate increased number of satellite glial cells/DRG neuron. Collectively, our data suggests that sAPPa may mediate pathways in the development of key neuropathological hallmarks of type 1 diabetes and may represent a novel target for future therapeutic interventions. This data also suggest that the effects observed may be glial-derived.

Disclosures: G.L. Odero: None. **B.D. Aulston:** None. **D.R. Smith:** None. **G.W. Glazner:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.24/EE8

Topic: D.03. Somatosensation: Pain

Support: R43CA206796
R43DA047106

Title: Loss of heat pain sensitivity in patients with diabetic and chemotherapy-induced neuropathic pain is nociceptor fiber specific and spontaneous pain may not assess by contact or radiant heat

Authors: *M. I. NEMENOV[1,2], M. KLUKINOV[2], D. C. YEOMANS[3], M. SCHMELZ[4]
[1]Lasmed LLC, Mountain View, CA; [2]Anesthesia, Stanford Univ., Palo Alto, CA; [3]Stanford Univ., Stanford, CA; [4]Heidelberg Univ., Mannheim, Germany

Abstract: Denervation of epidermal nociceptors leads to pain sensitivity loss to contact or radiant heat in the area where patients experience spontaneous neuropathic pain (NP). Likely because of this paradox, no correlation between NP and heat pain thresholds are found, in contrast with inflammatory pain states. We found that a group of C fibers is sensitized to heat similarly as in inflammatory pain [1] and the loss of pain sensitivity in the NP patients is nociceptors type specific [2]. These novel findings may explain why spontaneous NP may be observed in the area of pain sensory loss in diabetic and chemotherapy-induced NP patients. Thus, sensitized and spontaneously active C mechano-insensitive (CMi) nociceptors are likely responsible for spontaneous NP but not accessible by contact or radiant heat. In contrast, the loss

of readily accessible C and Aδ polymodal nociceptors is responsible for loss of heat pain sensitivity. Heat sensitive CMi as well as C polymodal and Aδ nociceptors are trpv1 positive and thus have same thresholds to heat. The inaccessibility of CMi compared to polymodal nociceptors may be explained by their deeper location. **We hypothesize that the CMi are located mainly in subepidermal and dermal tissue unlike C and A δ polymodal nociceptors which are mainly epidermal.** To test this we recruited 12 healthy volunteers without a history of peripheral neuropathy. Activation of CMi fibers was assessed by measuring the flare response to heat, as CMi fibers are solely responsible for this. Activation of the CMi and pain thresholds were defined in normal skin of 33 °C and in skin cooled to 22 °C. The skin cooling numbs epidermal fibers and mimics heat sensory loss in the patients. Diode Laser pulses (LasMed, CA) that produces deep skin heating and selective activation of C fibers were used. Neurogenic flare was documented by perfusion recording (Perimed, Sweden). Temperature was monitored by thermal camera (Flir, USA). Skin cooling was performed by controllable CO_2 gas spray. ***Activation of CMi nociceptors as assessed by induction of neurogenic flare response required less energy when compared to induction of pain, in particular after superficial cooling, suggesting a matching of stimulation depth of DL and CMi nociceptors location.*** Such matching may explain abnormally low C fibers pain thresholds in the patients as they have few epidermal polymodal fibers but deeper CMi fibers may be relatively intact and sensitized [1,2]. 1. Nemenov et al. Heating of deeper skin layers might detect spontaneously active heat-sensitized nociceptors. SFN 2015. 2. Moeller et al. Sensory Small Fiber Function Differentially Assessed with Diode Laser QST in Painful Neuropathy. Pain Medicine 2013.

Disclosures: M.I. Nemenov: A. Employment/Salary (full or part-time):; LasMed LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); LasMed LLC. **M. Klukinov:** None. **D.C. Yeomans:** None. **M. Schmelz:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.25/EE9

Topic: D.03. Somatosensation: Pain

Support: NIH Grant T32 DE014318
San Antonio Area Foundation

Title: A novel role of oxidized omega-6 polyunsaturated fatty acids in diabetic pain

Authors: *P. M. LOCOCO, A. R. FURR, D. A. ARRIS, K. M. HARGREAVES
Univ. of Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX

Abstract: Diabetic neuropathy (DN), one of the most common, taxing complications of type 2 diabetes (T2D), arises from persistent metabolic abnormalities that damage the peripheral nerves, especially sensory afferent fibers that innervate the feet and hands, leading to debilitating numbness, neuropathic pain and other sensorimotor symptoms. There is an urgent need to delineate mechanisms underlying DN and identify novel treatments, as an effective therapy does not exist. We demonstrated previously that oxidized metabolites of linoleic acid (LA), a prominent omega-6 polyunsaturated fatty acid (PUFA), regulate TRPV1 and TRPA1 activity in nociceptors and trigger pain behaviors. The purpose of this study is to investigate the contribution of omega-6 PUFAs to diabetic pain. Using db/db mice as a model of T2D and dyslipidemia, we first characterized the development of DN by monitoring changes in nociceptive thresholds to various stimuli. By 16 weeks of age, db/db mice developed mechanical and cold allodynia, but sensitivities to heat, pinprick, and brush were unchanged. To determine whether acute oxidation of omega-6 PUFAs affected neuronal responsiveness, we administered a single intraplantar injection of LA (1 mg) to the mice. 30 min post-injection, LA exacerbated the mechanical hypersensitivity in db/db mice, suggesting a likely interaction between omega-6 PUFAs and/or their metabolites with afferent neurons in the hindpaw. We next asked whether pharmacological inhibition of omega-6 PUFA-oxidizing enzymes affected mechanical thresholds. Ketoconazole (10 mg/kg, i.p.), voriconazole (10 mg/kg, i.p.), or vehicle were injected daily for 4 days. Mechanical thresholds were measured the day before the first injection and the day after the last injection. Interestingly, both ketoconazole and voriconazole treatment attenuated the mechanical allodynia in db/db mice, suggesting that enzymatic oxidation of omega-6 PUFAs contributes to DN. We also performed single-fiber electrophysiology using isolated glabrous skin-tibial nerve preparations to measure spontaneous activity and changes in stimulus-evoked functional responsiveness of primary afferent fibers innervating the glabrous paw skin. Nociceptive fibers from db/db mice exhibited an increase in spontaneous firing as well as a leftward shift in mechanical sensitivity. Collectively, these data indicate a novel role for omega-6 PUFAs in T2D-associated pain.

Disclosures: P.M. LoCoco: None. **A.R. Furr:** None. **D.A. Arris:** None. **K.M. Hargreaves:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.26/EE10

Topic: D.03. Somatosensation: Pain

Support: NIH/NIDCR R01DE025393

Title: Spatial organization of oral tongue cancer invasion into peripheral nerves in a murine oral carcinogenesis model

Authors: *A. BHATTACHARYA[1,2], R. VEERAMACHANENI[3], B. L. SCHMIDT[2], D. G. ALBERTSON[2]
[2]Bluestone Ctr. for Clin. Research, Oral and Maxillofacial Surgery, [3]Bluestone Ctr. for Clin. Res., [1]NYU Col. of Dent., New York, NY

Abstract: Perineural invasion (PNI) is associated with increased risk for tumor recurrence, increased risk for cervical node metastasis and decreased overall patient survival in oral cavity squamous cell carcinoma (SCC). Oral SCC patients with PNI also report function related pain which is not relieved by opioids (the current standard of care). PNI is classically defined as cancer cell "invasion in, around, and through peripheral nerves." Although the College of American Pathologists Oral Cavity Cancer Protocol (2017) recommends reporting the presence and extent of perineural invasion in a pathology report, pathologists differ in their interpretation of this prognostic histologic feature. Furthermore, PNI is evaluated only in surgical resection specimens and not in preoperative biopsy tissue, and therefore evaluation of this critical parameter is not available for surgical treatment planning. The 4-nitroquinoline-1-oxide (4NQO) oral carcinogenesis model recapitulates histopathological features of human oral SCC, including invasion, tumor heterogeneity, PNI and lymphovascular invasion. A subset of tongue SCC shows extensive PNI that can be defined by specific histological patterns of nerve-cancer cell associations (e.g., complete vs incomplete encirclement of nerve, tangential contact). The 4NQO model offers an opportunity to develop a three dimensional map of oral SCC-nerve associations from serial sections. These maps can guide pathological analysis of human tongue SCC.

Disclosures: A. Bhattacharya: None. **R. Veeramachaneni:** None. **B.L. Schmidt:** None. **D.G. Albertson:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.27/EE11

Topic: D.03. Somatosensation: Pain

Support: K22NS096030

Title: Sex differences in cell-specific toll-like receptor 4 signaling on neuropathic pain development

Authors: *T. A. SZABO-PARDI, N. M. AGALAVE, K. A. LINDQUIST, M. D. BURTON
Brain and Behavioral Sci., Univ. of Texas At Dallas, Richardson, TX

Abstract: Chronic pain is a widespread burden that affects millions of people worldwide. It is incumbent to identify and understand the cellular mechanisms involved so that we may develop effective therapeutics to combat the growing opioid epidemic. Danger-associated molecular patterns (DAMPs) released from cells following traumatic peripheral nerve injury promote pain plasticity underlying chronic pain. High-mobility group-box-1 is a DAMP produced after injury and activates toll-like receptor-4 (TLR4). TLR4 is a pattern-recognition receptor expressed on peripheral sensory neurons and immune cells whose activation promotes pain states. Understanding how different cell types respond to TLR4 activation could lead to a better grasp on the mechanisms of pain plasticity and lead to novel therapeutic insights. We hypothesize that TLR4 acting on macrophages contributes to the development of neuropathic pain in male mice as opposed to sensory neurons in female mice. Here we have employed a transgenic model that allows for Cre-mediated deletion of a floxed TLR4 allele, utilizing the $Na_V1.8$ and Lysozyme M promoters to drive *cre* expression in peripheral nociceptors or macrophages, respectively. We implemented a spared-nerve injury model and subjected adult male and female transgenic mice to von Frey mechanical tests and cold allodynia measures. In addition, we assayed changes in HMGB1 expression within the dorsal horn of the spinal cord 3 days following nerve injury in wild-type mice. We find that TLR4 removed from $Na_V1.8^+$ sensory neurons confers a reduction in mechanical hypersensitivity at day 3 and 5 post-surgery in female, but not male mice. In contrast, we find that TLR4 removed from $LysM^+$ macrophages reduces mechanical hypersensitivity at day 3 and 5 post-surgery in male, but not female mice. There were no differences in cold allodynia. We see elevated expression of HMGB1 in deeper laminae in females after injury, versus superficial laminae in males. We have observed a robust, sexually dimorphic behavioral effect when TLR4 is removed from macrophages in males versus nociceptors in females. Our data shows that TLR4 acting on sensory neurons mediates development of neuropathic pain in females and TLR4 acting on macrophages mediates development of neuropathic pain in male mice.

Disclosures: T.A. Szabo-Pardi: None. **N.M. Agalave:** None. **K.A. Lindquist:** None. **M.D. Burton:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.28/EE12

Topic: D.03. Somatosensation: Pain

Support: The Chronic Pain Network (Northbridge)
Canadian Institute of Health Research

Title: Development of pain hypersensitivity in a model of non-compressive disc herniation

Authors: M. M. MULEY, Y. TU, *M. W. SALTER
Neurosciences & Mental Hlth. Program, Hosp. for Sick Children, Toronto, ON, Canada

Abstract: OBJECTIVE: Disc-herniation can be caused by biochemical inflammation and mechanical deformation. Here, we have developed a mouse model of non-compressive disc herniation to assess the contribution of inflammatory cells in the development of changes in pain behavior. **METHODS:** Nucleus pulposus (NP) material collected from littermate tail was placed on the sciatic nerve of C57BL/6 mice (22-36g). In sham animals, only the sciatic nerve was exposed. von Frey algesiometry and dynamic weight-bearing were measured at every other day over the subsequent two weeks. In a separate cohort, immunohistochemistry on day 7 and 21 was used to study infiltration of inflammatory cells in nerve and ATF3 expression in the dorsal root ganglion (DRG). **RESULTS:** Heterotopic placement of NP onto the sciatic nerve induced mechanical sensitivity at day 1 ($P < 0.0001$) compared to sham, and the mechanical sensitivity persisted for up to 11 days ($P < 0.05$). We observed weight-bearing deficits in the ipsilateral hind paw at day 5 ($P < 0.05$) as compared to sham. Immunohistochemical analysis revealed intraneural macrophage (F4/80) infiltration compared with sham controls, with localized and most infiltration at nerve observed at 1 week ($P < 0.05$), and resolved by day 21. Animals exposed to NP did not show ATF3 expression within DRG. **CONCLUSIONS:** These results demonstrate that surgical placement of heterotopic NP onto the sciatic nerve triggers a behavioral pain phenotype and transient inflammatory response characterized by infiltration of inflammatory cells. Therefore, blocking inflammation may be a viable strategy in treating radiculopathy associated with disc herniation.

Disclosures: M.M. Muley: None. **Y. Tu:** None. **M.W. Salter:** None.

Poster

666. Peripheral Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 666.29/EE13

Topic: B.12. Demyelinating Disorders

Support: Bundesministerium für Bildung und Forschung

Title: Reduced skin innervation in Charcot-Marie-Tooth disease type 1A patients

Authors: *B. HARTMANNSBERGER[1], K. DOPPLER[1], J. STAUBER[2], B. SCHLOTTER-WEIGEL[2], P. YOUNG[3], C. L. SOMMER[1]
[1]Dept. of Neurol., Univ. of Wuerzburg, Wuerzburg, Germany; [2]Ludwig Maximilian Univ. of Munich, Munich, Germany; [3]Univ. of Muenster, Muenster, Germany

Abstract: Background and Objective:
The most common hereditary neuropathy is Charcot-Marie-Tooth disease. The subtype with the highest prevalence of estimated 1:5,000 is CMT1A which is caused by a duplication of the PMP22 gene on chromosome 17p11. There is currently no treatment approved for CMT1A. However, there is a triplet medication called PXT3003 which is tested in clinical trials. Our aim is to provide objective and reproducible outcome criteria for future clinical trials. Therefore, we analyzed the cutaneous innervation and density of mechanoreceptors of skin punch biopsies of patients with CMT1A.

Methods:
Glabrous skin samples were taken from the index finger of 39 CMT1A patients, 16 small fiber neuropathy (SFN) patients, 7 chronic inflammatory demyelinating polyneuropathy (CIDP) patients and 43 healthy controls. CMTNSv2 scores of the CMT1A patients ranged from 3 (mild disease) to 27 (severe disease). Immunohistochemical double labeling was performed with anti-MBP (myelin marker), anti-S100 (to detect Meissner corpuscles (MCs)) and anti-cytokeratin20 (CK20, Merkel cells (MrkC) marker) combined with anti-PGP9.5 (axonal marker) on 40 µm thick cryosections. So far, we analyzed the density of MCs, MrkCs, free nerve endings in the epidermis and myelinated fiber bundles throughout the dermis by IHC staining.

Results:
Analyses of skin samples stained with anti-CK20 and anti-PGP9.5 showed a reduction of MrkC density in CMT patients compared to controls ($p=0.042$). Staining with anti-S100 and anti-PGP9.5 showed no reduction in MC density in CMT patients compared to controls. However, the ratio of samples without MCs was clearly higher in the CMT group (46%) than in the three other groups together (21%, $p=0.0003$). Dermal nerve bundle densities were not different between the groups for both bundles with and without myelinated fibers. Assessment of the intraepidermal nerve fiber densities (IENFD) revealed a reduction in CMT patients compared to all control groups (SFN: $p=0.056$, CIDP: $p=0.042$, Control: $p=0.005$). Moreover, the CMT-IENFD and the CMTNSv2 score were negatively correlated, meaning that more severely affected patients have fewer intraepidermal nerve fibers ($r=-0.400$, $p=0.013$).

Conclusions:
Our results show reduced skin innervation in CMT1A patients. In addition, our data suggest that skin innervation (IENFD) is reduced in CMT1A patients with high CMTNSv2 scores compared to patients with lower CMTNSv2 scores. This might provide a possible outcome marker for clinical trials. Further IHC labeling of proteins of the node of Ranvier will reveal more insight into the effect of CMT on nerve structures.

Disclosures: B. Hartmannsberger: None. **K. Doppler:** None. **J. Stauber:** None. **B. Schlotter-Weigel:** None. **P. Young:** None. **C.L. Sommer:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.01/EE14

Topic: D.04. Somatosensation: Touch

Title: Development of inhibitory wiring specificity in mouse cerebral cortex

Authors: *A. G. GOUR, K. M. BOERGENS, P. LASERSTEIN, Y. HUA, M. HELMSTAEDTER
Dept. of Connectomics, Max Planck Inst. For Brain Res., Frankfurt, Germany

Abstract: The development of interneurons in the cerebral cortex has been studied for their migrational origin, time of integration into the cortical plate and electrophysiological properties. The connectomic development and the development of wiring specificity of interneurons is however still largely unknown. Here, we studied 3D EM datasets from the primary somatosensory cortex in mice at postnatal ages 7, 9, 14 and 28 days to map inhibitory connectomes over ontogenetic development. We find that the specificity of inhibitory axons for subcellular components of the postsynaptic neuron is already mutually exclusive at the earliest circuit stages, but the quantitative specificity of inhibitory wiring further increases over age. This development is dependent on the type of inhibitory target preference: the synapse specificity to apical dendrites develops first, followed by wiring specificity to somata, and finally to axon initial segments (AIS). These data provide a first quantification of connectomic specificity over development in the cerebral cortex, pointing towards differential mechanisms of synaptic specificity created by enhancement of target selection over age, and selective pruning of unspecific synapses.

Disclosures: A.G. Gour: None. **K.M. Boergens:** None. **P. Laserstein:** None. **Y. Hua:** None. **M. Helmstaedter:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.02/FF1

Topic: D.04. Somatosensation: Touch

Title: Connectomic study of mice barrel cortex after sensory deprivation in adult

Authors: *K. SONG, M. HELMSTAEDTER
Max-Planck Inst. For Brain Res., Frankfurt Am Main, Germany

Abstract: Whisker trimming can lead to substantial structural plasticity changes in the adult barrel cortex. In order to examine the structural plasticity at a finer scale, we sought to compare the connectomes between mice that were whisker trimmed vs. normal control. Starting at P28, the experimental mice underwent 4 weeks trimming that remove the A,B,C rows of whiskers on both side every second day. By correlative imaging of light microscope and electron microscope, we are able to sample the targeted barrels with high precision; as the mice barrels are about 250 μm in size, we are able to have 2~3 targeted barrels in one sample (1 mm in diameter). This is a first step towards understanding the connectomic changes induced by sensory deprivation in barrel cortex.

Disclosures: K. Song: None. **M. Helmstaedter:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.03/FF2

Topic: D.04. Somatosensation: Touch

Title: The inhibitory input connectome of apical tuft dendrites in mouse cerebral cortex

Authors: *A. KARIMI, J. ODENTHAL, F. DRAWITSCH, K. BOERGENS, M. HELMSTAEDTER
Connectomics, MPI Brain Res., Frankfurt, Germany

Abstract: All pyramidal cells, the principal neurons of the cerebral cortex, send large apical dendrites into cortical layer 1, where long-range inputs from higher-order brain areas are thought to converge onto the pyramidal cells' tuft dendrites. The synaptic input from these sources has been shown to permit regenerative electrical activity, which can yield action potential output of the pyramidal cell that is dependent on the coincidence of basal and distal inputs - interpretable as a cellular binding mechanism. Importantly, these distal dendritic input zones are thought to be controlled by powerful inhibitory inputs, in place to prevent such regenerative activity. Here, we used 3-D electron microscopy to acquire datasets from mouse somatosensory, secondary visual, anterior cingulate and posterior parietal cortices to study the inhibitory connectome of distal apical tufts. To our surprise, we find that only supragranular pyramidal cell dendrites, but not the main bifurcations of deep-layer pyramidal cells are substantially innervated by inhibitory inputs. Rather, deep-layer pyramidal cells receive substantial inhibitory input at the most distal tips of their apical tufts. These results imply that the apical tuft of the main cortical output neurons is largely unhinged, allowing powerful excitation. Furthermore the inhibitory control of apical

dendrites is highly selective between supragranular and deeper-layer principal neurons, with axons selectively innervating supra- but not infragranular apical dendrites and vice versa. These differential inhibitory connectomic structures are preserved between cortices of early sensory and higher-order type, indicating a general wiring mechanism in the upper layers of the cerebral cortex.

Disclosures: A. Karimi: None. **J. Odenthal:** None. **F. Drawitsch:** None. **K. Boergens:** None. **M. Helmstaedter:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.04/FF3

Topic: D.04. Somatosensation: Touch

Support: Max Planck Society

Title: FluoEM: virtual labeling of axons in 3D EM data for long-range connectomics

Authors: *F. P. DRAWITSCH, A. KARIMI, K. M. BOERGENS, M. HELMSTAEDTER
Max Planck Inst. for Brain Res., Frankfurt Am Main, Germany

Abstract: Current volume electron microscopy methods allowing for dense neuronal circuit reconstruction are so far limited to dataset volumes a few hundred micrometers in extent. However, since most neuronal circuits receive substantial non-local input, the projection sources for a large fraction of local synapses remain unknown in such data. Most correlative labeling strategies applied so far to alleviate this limitation rely on label conversion which is technically challenging and augments label space only slightly because of the limited EM color space. Here, we present FluoEM, a set of experimental and computational methods allowing for the direct identification of fluorescently labeled axons in EM without label conversion. Instead, we computationally match reconstructed neurites resulting in a virtual labeling of EM axons and allowing us to utilize the rich color palette of available fluorophores. We then apply FluoEM to explore the specificity of long-range projections from primary motor- (M1) and secondary somatosensory (S2) cortex impinging in L1 on the apical dendrites of primary somatosensory (S1) barrel cortex pyramidal neurons.

Disclosures: F.P. Drawitsch: None. **A. Karimi:** None. **K.M. Boergens:** None. **M. Helmstaedter:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.05/FF4

Topic: D.04. Somatosensation: Touch

Title: High-throughput connectomics in mouse barrel cortex

Authors: *M. SCHURR, J. STRAEHLE, L. DADASHEV, A. MOTTA, H. KEBIRI, N. SHETTAR, M. HELMSTAEDTER
MPI For Brain Res., Frankfurt, Germany

Abstract: Dense mapping of neuronal circuits at single-cell resolution in a sufficiently large volume requires 3D imaging techniques which are able to bridge five to six orders of magnitude. Currently, comprehensive EM-based connectomic analysis is still hampered by the size and number of available datasets. The effective acquisition rate of conventional single-beam SEMs is ultimately limited by the scan speed. Data rates up to 6 $MVxs^{-1}$ have been reported (Schmidt et al, 2017). However, even at 6 $MVxs^{-1}$ imaging of a cubic millimeter of neuronal tissue at nanometer resolution would take several years. Here we report the application of a 61 beam MultiSEM setup in combination with the ATUMtome approach (Hayworth et al, 2006) for high-throughput connectomics in mouse barrel cortex. Taking into account overheads caused by stage settling time, automated focusing routines and wafer calibration, data rates were pushed by two orders of magnitude up to 237 $MVxs^{-1}$ at a voxel size of 4 nm x 4 nm x 35 nm. Together with an appropriate data infrastructure to process petabytes of data this enables connectomic screening of a cubic millimeter within only three to four months expected time.

Disclosures: M. Schurr: None. **J. Straehle:** None. **L. Dadashev:** None. **A. Motta:** None. **H. Kebiri:** None. **N. Shettar:** None. **M. Helmstaedter:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.06/FF5

Topic: D.04. Somatosensation: Touch

Title: Deep learning for axon tracing in high-resolution connectomics

Authors: *M. SCHMIDT, A. MOTTA, B. STAFFLER, M. BERNING, M. HELMSTAEDTER
MPI Brain Res., Frankfurt Am Main, Germany

Abstract: Mapping neuronal wires for a mechanistic understanding of computation in the brain is a major goal of high-resolution connectomics. While acquisition of mm^3-sized 3D electron microscopy datasets is becoming feasible, axon reconstruction remains the main bottleneck. Here, we present a new framework to automatically trace axons in 3D-EM data, where a convolutional neural network is trained end to end in a supervised fashion to predict neurite continuation from EM images. Integration of the prediction and application of the network in a recurrent manner yields a sparse skeleton representation of axonal branches. Application of this framework on linear branches of axons in a 3D-EM dataset from mouse primary somatosensory cortex layer 4 results in error rates that make it plausible to deploy the framework in conjunction with existing automated reconstruction approaches in order to further reduce the human annotation needs in connectomics.

Disclosures: M. Schmidt: None. **A. Motta:** None. **B. Staffler:** None. **M. Berning:** None. **M. Helmstaedter:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.07/FF6

Topic: D.04. Somatosensation: Touch

Title: Comparative connectomics in the mammalian cerebral cortex

Authors: *S. LOOMBA, J. STRAEHLE, K. BOERGENS, M. HELMSTAEDTER
Max Planck Inst. For Brain Res., Frankfurt Am Main, Germany

Abstract: The advancements in subcellular-resolution connectomics and the reconstruction of neurons and their synaptic connectivity are opening the possibilities to find general principles of wiring across a wide range of brain systems. Here we report a comparative connectomics analysis of serial block-face electron microscopy (EM) data from mouse and rat. For this SegEM (Berning et al 2015 Neuron) for automated dense reconstruction and analysis of the 3D EM data had to be extended. We ask whether a 3-fold increase in neuron number between mouse and rat is accompanied by connectomic alterations along the species axis. We are currently extending this analysis to non-human primate and human tissue.

Disclosures: S. Loomba: None. **J. Straehle:** None. **K. Boergens:** None. **M. Helmstaedter:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.08/FF7

Topic: D.04. Somatosensation: Touch

Title: Dense connectomic reconstruction in layer 4 of the somatosensory cortex

Authors: *A. MOTTA, M. BERNING, K. M. BOERGENS, B. STAFFLER, M. BEINING, S. LOOMBA, C. SCHRAMM, H. WISSLER, M. HELMSTAEDTER
Connectomics, Max Planck Inst. For Brain Res., Frankfurt, Germany

Abstract: The dense circuit structure in the mammalian cerebral cortex is still unknown. With developments in 3-dimensional (3D) electron microscopy, the imaging of sizeable volumes of neuropil has become possible. The dense reconstruction of connectomes from such image data, however, is still the limiting step in connectomics. Here, we report the dense reconsruction of a volume of about 500,000 cubic micron from layer 4 of mouse barrel cortex, about 250 times larger than previous dense reconstructions from the mammalian cerebral cortex. Using a novel reconstruction technique, FocusEM, we were able to obtain a total of 600 millimeters of dendrites and about 2 meters of axons investing only about 3,000 human work hours, thus about 30 times more efficient than previous dense reconstructions from the mammalian brain. We used this dense connectomic data for the quantitative analysis of subcellular synaptic target specificity; we determine the maximum fraction of geometrically explainable connectivity and extract a connectomic snapshot of the plasticity history of the circuit.
AM, MB, KMB, and BS contributed equally to this work.

Disclosures: A. Motta: None. **M. Berning:** None. **K.M. Boergens:** None. **B. Staffler:** None. **M. Beining:** None. **S. Loomba:** None. **C. Schramm:** None. **H. Wissler:** None. **M. Helmstaedter:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.09/FF8

Topic: D.04. Somatosensation: Touch

Support: NSF Graduate Research Fellowship

NIH Grant F32NS096819
NIH Grant R01NS094659

Title: A parametric texture discrimination task reveals an essential role of primary somatosensory cortex in mice

Authors: *J. PARK[1], C. RODGERS[3], Y. HONG[2], R. M. BRUNO[1]
[1]Neurosci., [2]Dept. of Neurosci., Columbia Univ., New York, NY; [3]Columbia Univ. Med. Ctr., New York, NY

Abstract: Touch is a fundamental part of our sensory perception, yet our understanding of the neural circuitry that underlies it is limited. For example, the primary somatosensory cortex (S1) has long been assumed to play a crucial role in tactile processing. Yet recent and surprising results from our lab show S1 to be completely unnecessary for simple whisker-based tactile tasks, such as detecting the presence of an object. This corroborates previous findings in other primary sensory areas. It is possible, however, that more complex tasks with greater computational demands require the cortex. To better understand S1 function and circuitry, we have developed a two-alternative forced choice paradigm for head-fixed mice in which the animals discriminate textures using their whiskers. Unlike many previous studies that use sandpaper stimuli, we have machined plastic grooved textures to precisely manipulate and quantify various parameters that determine the perception of roughness. The mice readily learn to distinguish textures at various distances and orientations using all or even just one whisker. We have confirmed by trimming or physically blocking their whiskers that this task is completely whisker-dependent. We find that lesioning S1 reduces their performance to chance, demonstrating that within the tactile domain, texture discrimination is a cortex-dependent task. This result highlights the need to reexamine cortical function in tactile and other sensory modalities. Using this S1-dependent texture discrimination task, future work is aimed at examining the underlying neural mechanisms that encode tactile discrimination.

Disclosures: J. Park: None. **C. Rodgers:** None. **Y. Hong:** None. **R.M. Bruno:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.10/FF9

Topic: D.04. Somatosensation: Touch

Support: NIH R01 NS094659
NIH NINDS F32 NS0055488

Title: Differential roles of cortex and striatum in tactile detection

Authors: *Y. HONG, B. C. PIL, R. BRUNO
Dept. of Neurosci., Columbia Univ., New York, NY

Abstract: Numerous studies have sought to establish whether the primary sensory cortex (S1) is required for sensory detection behaviors, but with conflicting results. In mice trained to perform a whisker-mediated detection task, we demonstrate that transient S1 inactivation initially alters both whisking motor output and sensory threshold, resulting in impaired sensory detection. However, in S1-lesioned animals, these effects are only momentary, as the subject recovers after a single session of re-exposure to the task, bypassing any requirement for S1 in sensory detection. What is the mechanism by which transient, but not chronic, inactivation disrupts detection behavior? One hypothesis is that sudden loss of activity in S1 temporarily disrupts connected downstream areas that may themselves be essential for task performance, but that over a short period, recovery of the downstream area enables resumption of detection abilities. An essential first step in understanding tactile detection is to delineate the key pathways that can mediate detection behaviors in in the absence of S1. We narrow down the essential S1 targets by taking advantage of available mouse transgenic Cre recombinase subset lines that label cells in distinct cortical laminae. We inactivated different subsets of cortical neurons in S1 during the detection task to determine which conditions recapitulate the transient behavioral deficit observed during inactivation of all cortical layers. We find that only a few subset lines yielded a deficit in detection behavior. These had one major subcortical target in common: the dorsal striatum. Indeed, while S1-lesioned animals recovery rapidly recover behavioral performance, additional damage to the striatum permanently impaired detection behavior. Together, our results implicate the dorsal striatum, rather than S1, as a key player in mediating sensory detection for sensory perception.

Disclosures: Y. Hong: None. **B.C. Pil:** None. **R. Bruno:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.11/FF10

Topic: D.04. Somatosensation: Touch

Title: Stabilization of cortical neuron ensembles by sensory association learning

Authors: *J. LEE, S. M. BERNHARD, N. J. AUDETTE, A. L. BARTH
Dept. of Biol. Sci., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Sensory features are thought to be encoded by specific ensembles of neurons, such as orientation cells in visual cortex. To determine whether experience could alter neuronal ensembles in somatosensory cortex, we monitored the distribution and percentage of activated

neurons in fosGFP transgenic mice during multi-whisker sensory association training. We trained the mice to associate gentle air puff stimulation to the whiskers with water reward. Since fosGFP-positive neurons are known to show large responses to multi-whisker stimulation, we hypothesized that the number of fosGFP-positive neurons would increase by this training. We imaged fosGFP-positive neurons in layer 2/3 of barrel cortex through cranial window with 2-photon in vivo microscopy, once before and once after training. When we compared before and after, we found that training does not change the overall number of fosGFP-positive neurons. But when we looked at individual cell's fosGFP expression level, there were more cells with stable fosGFP expression over two days. Therefore, we found that multi-whisker sensory association training stabilizes multi-whisker representing ensembles, which may play a role in learning.

Disclosures: J. Lee: None. **S.M. Bernhard:** None. **N.J. Audette:** None. **A.L. Barth:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.12/FF11

Topic: D.04. Somatosensation: Touch

Support: NIH
CMU-IISc Brainhub

Title: Anatomical correlates of learning at Pom thalamocortical inputs in the neocortex

Authors: *A. RAY[1,4], N. J. AUDETTE[1,4], D. A. KULJIS[1,4,5], M. MATSUSHITA[1,6], M. P. BRUCHEZ[1,2,3], A. L. BARTH[1,4]
[1]Biol. Sci., [2]Chem., [3]Mol. Biosensors and Imaging Ctr., Carnegie Mellon Univ., Pittsburgh, PA; [4]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [5]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [6]Dept. of Envrn. and Occup. Hlth. Sci., Univ. of Washington, Seattle, WA

Abstract: Thalamocortical inputs to neocortical circuits can be altered during sensory learning. To determine the temporal and laminar sequence of changes in neuronal response properties during learning, we designed an automated homecage system for sensory association training in mice, using a gentle airpuff coupled to a water reward. Electrophysiological recordings from pyramidal (Pyr) neurons in somatosensory (barrel) cortex revealed that optogenetic stimulation of Pom thalamic inputs initiated increased activity across the neocortical column after 24 hr of training. Electrophysiological responses to Pom stimulation were enhanced in L5 neurons, due to an increase in postsynaptic quantal EPSC amplitude. To examine training-dependent changes in the anatomical distribution and morphological properties of Pom synapses, we expressed a synapse-labeling fluorophore (FAPpost) in L5 Pyr neurons for quantitative analysis. Alignment of GFP-labeled Pom inputs with postsynaptic sites on L5 Pyr neurons revealed training-

dependent differences in the density and location of Pom inputs across the L5 dendritic arbor. The fluorescent properties of postsynaptic sites assigned to Pom inputs were also evaluated for changes in synaptic labeling intensity, shape, and organization. The convergence of electrophysiological and anatomical data indicate that Pom inputs undergo significant plasticity during sensory learning that may be localized to specific cell types and subcellular compartments in neocortex. High-throughput synapse labeling and quantitative analysis provide a means to study structural correlates of synaptic plasticity, driving new and testable hypotheses about synaptic reorganization during learning.

Disclosures: A. Ray: None. **N.J. Audette:** None. **D.A. Kuljis:** None. **M. Matsushita:** None. **M.P. Bruchez:** None. **A.L. Barth:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.13/FF12

Topic: D.04. Somatosensation: Touch

Support: Swiss National Science Foundation (31003A-149858)
European Research Council (ERC Advanced Grant BRAINCOMPATH, project 670757)
Edmond and Lily Safra Center for Brain Sciences (ELSC) postdoctoral fellowship
EMBO long-term postdoctoral fellowship (ALTF_1077-2014)
Mari-Curie Individual Fellowship (659719-AG-GF)

Title: Refinement of spatiotemporal cortical dynamics in mice learning to discriminate between two textures

Authors: *A. GILAD, F. HELMCHEN
Brain Res. Inst., Univ. of Zurich, Zuerich, Switzerland

Abstract: The neocortex is crucial in learning a new behavioral task. However, how different parts of the neocortex contribute to the learning process remains largely unknown. Here, we trained head-restrained transgenic mice expressing GCaMP6f in layer 2/3 excitatory neurons in a ‘go/no-go’ texture discrimination task. A trial started with an auditory cue after which either a ‘go’ or a ‘no-go’ sandpaper texture approached the mouse’s whisker pad. Mice gradually learn to lick to the go texture (‘hit’) and withhold licking to the no-go texture (‘CR’). Throughout learning we imaged calcium signals across large parts of the cortex. During learning a consistent flow of activation that started in auditory cortex (A1) in response to the auditory cue, shifting to rostrolateral association area (RL) as the texture approaches the mouse, and then spreading to the barrel cortex (S1BC) when the texture touches the whiskers. The strength of this flow was

positively correlated with the mouse's learning curve, i.e. responses in A1, RL and S1BC are enhanced while the mouse gains expertise. In addition, discrimination between hit and CR trials gradually built up in S1BC during learning and appeared only during the whisker touch period. We also observe a spatial refinement of the activation in association areas. Naïve mice displayed responses to the approaching texture in many association areas, including RL, posterior medial are (PM), and primary visual cortex. In expert mice cortical responses were spatially confined to RL whereas PM decreased its activity with learning. These results imply that during learning the cortex refines spatiotemporal processing to highlight behavior-related integration paths while deemphasizing irrelevant ones.

Disclosures: A. Gilad: None. **F. Helmchen:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.14/FF13

Topic: D.04. Somatosensation: Touch

Support: BBSRC SWBio DTP Studentship

Title: Discrimination learning with tactile stimuli in rodents

Authors: *N. PACCHIARINI[1], R. C. HONEY[1], K. D. FOX[2]
[1]Sch. of Psychology, [2]Biosci., Cardiff Univ., Cardiff, United Kingdom

Abstract: The barrel cortex lies within the somatosensory cortex and processes information from the vibrissae. While a great deal is known about the anatomy, physiology and plasticity of the barrel cortex, less is known about its role in tactile discrimination and learning. The experiments reported here are aimed at investigating whether the barrel cortex is involved in discrimination learning with textured surfaces using a range of novel testing procedures, including a modified two-choice digging task (Chuang, Huang, and Hsueh, 2014). The chemogenetic DREADD system was used to test whether the barrel cortex is required for discrimination learning. In the two-choice digging task, a food reward was consistently buried in one sawdust filled bowl that was differentiated from the second bowl by whether its outer surface texture was smooth or ridged. Ten-week old mice were trained to locate the reward by touch in a room lit only with red light in which odours had been masked. Our results show that mice learn the task rapidly within one day and retain the memory of which texture was rewarded the following day. Whisker trimming reduced the animal's ability to perform the texture task to chance levels; however, the same mice were able to successfully perform the task two weeks later, when their whiskers had regrown. Additionally, whisker trimming did not affect task performance when the relevant stimulus was odour based. Further experiments show that if the barrel cortex neurones express

virally introduced DREADDs, mice are unable to learn the task following systemic injection with CNO (4mg/kg). CNO administered at the same dose in mice lacking DREADD expression were able to learn the task. Future experiments will allow us to observe structural plasticity during this period of rapid learning.

Disclosures: N. Pacchiarini: None. **R.C. Honey:** None. **K.D. Fox:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.15/FF14

Topic: D.04. Somatosensation: Touch

Support: European Union's Horiuon 2020
Human Brain Project
Deutsche Forschungsgemeinschaft

Title: The spatio-temporal dynamics of bilateral whisking in a touch task: Effect of optogenetic activation of somatosensory and motor cortices

Authors: *M. STAAB, K. SEHARA[1], S. DOMINIAK[3], M. E. LARKUM[2], R. N. SACHDEV[4]
[1]Inst. of Biol., [2]Humboldt Univ. of Berlin, Berlin, Germany; [3]Humboldt-Universität zu Berlin, Berlin, Germany; [4]Charite-Berlin, Berlin, Germany

Abstract: Movement is the result of complex interplay of activity in a large number of sensory and motor circuits. The whisker system is a model sensory and motor system, where individual whiskers are associated with intrinsic muscles, and furthermore, depending on the behavioral context, the motion of whiskers can be bilaterally synchronized or asymmetric. Here we trained head-fixed Nex-cre chanelrhodopsin mice (n=3) to perform a simple auditory-go-cue triggered movement that brought the C2 whisker into contact with a sensor. The C1 and C2 whisker on the right side, the contact side, and C2 whisker on the left side were painted and tracked offline using Image J macros. Bilateral tracking of whisker motion revealed: 1) the correlation between side to side motion of the whiskers was behavioral state -- i.e. cue onset, movement onset or licking -- dependent; the frequency bands in the correlation and the extent of motion, varied with state; 2) the main whisker used to touch the sensor began movement earlier than the other whiskers, and whiskers on the non-contact side, moved to a greater extent; 3) the effect of M1 and S1 stimulation on the side to side correlation varied from trial to trial but stimulation altered the side to side phase lag-lead relationship, and could even completely abolish correlations. Taken together our results show that cortical control of whisker motion is complex and the side to side motion of whiskers change dynamically.

Disclosures: M. Staab: None. **K. Sehara:** None. **S. Dominiak:** None. **M.E. Larkum:** None. **R.N. Sachdev:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.16/FF15

Topic: D.04. Somatosensation: Touch

Title: Rapid learning in a whisker-dependent sensory association task using homecage automated training

Authors: *S. BERNHARD, N. J. AUDETTE, A. T. HODGE, A. BARTH
Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Automated, homecage behavioral training for rodents has many advantages: it is low stress, requires little interaction with the experimenter, and can be easily manipulated to adapt any experimental condition. We have developed an inexpensive, Arduino-based, homecage training apparatus for sensory association training in freely-moving mice using bulk whisker stimulation coupled to a water reward. Animals learn this task readily, within 1 day of training, and performance continues to improve over multiple training days. We examined the parameters that regulate task acquisition using different airpuff intensities, directions, and reward valence. Learning was assessed by comparing anticipatory licking for the stimulus compared to the no-stimulus (blank) trials. At high airpuff intensities, animals showed markedly less task participation and no difference in lick frequency between the rewarded and blank trials. Very weak airpuff intensities were not sufficient to generate learning behavior. At intermediate airpuff intensities, a majority of mice learned that the airpuff predicted the water reward, showing increased licking after the airpuff stimulus and suppressing licking for blank trials. Mice learned to discriminate between multiple directions of airpuff rapidly and accurately. Systematic reductions in the angular distance between rewarded and non-rewarded airpuff direction was examined and compared to learning trajectories for airpuff versus blank training regimens. Our results show that a tactile association task in an automated homecage environment can be monitored by anticipatory licking to reveal rapid and progressive behavioral change. These Arduino-based, automated mouse cages enable high-throughput training that facilitate analysis of large numbers of genetically modified mice with targeted manipulations of neural activity.

Disclosures: S. Bernhard: None. **N.J. Audette:** None. **A.T. Hodge:** None. **A. Barth:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.17/FF16

Topic: D.04. Somatosensation: Touch

Support: Wellcome Trust
BBSRC
ERC

Title: Sensory responsiveness of cortical neurons predicts their behavioral salience in an operant conditioning task

Authors: *H. W. DALGLEISH, A. M. PACKER, L. E. RUSSELL, M. HAUSSER
Wolfson Inst. for Biomed. Res., Univ. Col. London, London, United Kingdom

Abstract: Identifying which neurons are most important for driving behavior is central to our understanding of how the brain represents and evaluates information during decision-making. In sensory cortex, stimulation of small numbers of neurons can produce a behavioral report. However, it is unclear which neurons are endowed with the greatest power to drive such behavior. It has been difficult to address this question with traditional electrophysiological and optogenetic techniques since the populations of neurons most relevant for decision-making are hard to target. To overcome this, we have used an all-optical approach, combining two-photon calcium imaging and optogenetics, to enable targeted interrogation of functionally defined neurons in vivo during behavior. We first trained head-fixed mice to report the optogenetic activation of specific, functionally defined groups of hundreds of neurons in L2/3 barrel cortex. Within this initially trained population, targeted activation of subgroups of strongly sensory responsive neurons was better able to drive the learned behavior than activation of subgroups of weakly sensory responsive neurons. Furthermore, preliminary results suggest that the sensory response strength of non-photostimulated neurons in the local network recruited during photostimulation epochs correlates with the sensory response strength of neurons that were photostimulated. These results demonstrate that the sensory response strength of neurons in mouse barrel cortex predicts their power to drive subsequent learned behaviour, and suggest that sensory neurons that are more informative about the outside world may also be privileged in their ability to broadcast that information and influence behavior.

Disclosures: H.W. Dalgleish: None. **A.M. Packer:** None. **L.E. Russell:** None. **M. Hausser:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.18/FF17

Topic: D.04. Somatosensation: Touch

Title: Effect of sensory associative learning on parvalbumin neuron plasticity in the barrel cortex

Authors: *E. PARK[1,2], D. A. KULJIS[1,2,3], M. P. BRUCHEZ[1,2,4], A. L. BARTH[1,2,3]
[2]Biol. Sci., [3]Ctr. for the Neural Basis of Cognition, [4]Mol. Biosensor and Imaging Ctr., [1]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: GABAergic parvalbumin (PV) neurons are a dominant source of inhibition to neocortical pyramidal (Pyr) neurons, and prior studies suggest that these inputs can be altered during learning. Here we examined evidence for anatomical changes in PV input to Pyr neurons in mouse somatosensory cortex during learning. We employed a novel postsynaptic fluorescent marker for synapses on PYR neurons that employs a neuroligin-1 trafficking motif (FAPpost) in mice where presynaptic PV neurons expressed YFP (PV-Cre x Ai3). PV inputs were aligned to postsynaptic fluorescent puncta for automated detection and quantitative analysis of PV inputs to Pyr neurons. Mice were trained to associate a gentle airpuff (sensory stimulus) with the reward (water). Labeled synapses on different compartments of the postsynaptic Pyr neuron were quantified using 3-dimensional detection and reconstruction (Imaris). While there was no change in PV inputs to layer 5 (L5) Pyr neurons, PV inputs to L2 Pyr neurons decreased after sensory association learning, particularly on the dendrites. Characterizing learning-dependent changes in PV inputs across the cortical column will enable a comprehensive understanding of how plasticity of inhibitory synapses in the brain is modified by experience.

Disclosures: E. Park: None. **D.A. Kuljis:** None. **M.P. Bruchez:** None. **A.L. Barth:** None.

Poster

667. Touch: Barrel Cortex II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 667.19/GG1

Topic: D.04. Somatosensation: Touch

Support: NIH Grant R01NS089652

Title: Sensorimotor specificity of decision-related activity in somatosensory cortex

Authors: *E. FINKEL, E. E. LUBIN, A. J. CHANG, J. Y. COHEN, D. H. O'CONNOR
Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Detection of a tactile stimulus is accompanied by increased firing rates of neurons in primary somatosensory (S1) cortex (e.g. Sachidhanandam et al., 2013; Yang et al., 2016). This enhanced activity begins hundreds of milliseconds before the report of the stimulus, and its optogenetic inhibition interferes with detection (Sachidhanandam et al., 2013). How such choice-related late activity relates to motor planning and attention is not currently understood. Here, we trained head-fixed mice (>15) on a novel cross-modal attention task, in which stimuli of different sensory modalities were associated with different movements. The task consisted of interleaved trials in which either a weak tactile stimulus (brief single-whisker deflection) or a weak visual stimulus (faint LED flash) was presented. In a "tactile block" of trials, mice were rewarded for reporting detection of the tactile stimulus by licking at a lickport while responses to the visual stimulus were unrewarded. Conversely, in a "visual block" of trials, mice were rewarded for detecting the visual stimulus by licking at a different lickport while responses to the tactile stimulus were unrewarded. Tactile blocks and visual blocks were alternated several times across each experimental session. After 3-4 weeks of training, mice learned to respond to the tactile stimulus and ignore the visual stimulus during tactile blocks, while ignoring the tactile stimulus and responding to the visual stimulus during visual blocks (~75% correct for each block type). We performed extracellular tetrode recordings from >2000 neurons in S1 barrel cortex of well-trained mice. 773 recorded S1 neurons showed significant choice-related activity. A large fraction of these neurons (~34%) showed higher evoked firing rates only in trials where the mouse detected the tactile stimulus and executed the associated licking response (tactile-hits). Other neurons (~21%) showed increased firing rates only when mice detected the visual stimulus and made the (different) associated licking response (visual-hits). The remaining ~45% of neurons showed increased firing rates in trials where the mouse detected either stimulus. Neurons showed similarly low levels of activation in trials where the mice failed to detect stimuli (misses) as in trials where they correctly ignored the stimuli (correct rejections). These data suggest that choice-related activity is associated with the upcoming movements required of the mouse to report its perceptual detection. Thus, S1 neurons encode a conjunction of motor and sensory variables.

Disclosures: E. Finkel: None. **E.E. Lubin:** None. **A.J. Chang:** None. **J.Y. Cohen:** None. **D.H. O'Connor:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.01/GG2

Topic: B.04. Ion Channels

Support: NSFC 31422027
NSFC 31371118
NSFC 31630090
NSFC 21375010
MSF 2015CB910102
MSF 2016YFA0500402
Young Thousand Talent Program

Title: The mechanically activated Piezo channels are sufficient for conferring specific modalities of mechanosensation

Authors: *M. ZHANG, B. XIAO
Sch. of Pharmaceut. Sci., Tsinghua Univ., Beijing City, China

Abstract: The mechanosensation of light-touch and proprioception, but not mechanical pain, requires a single mechanically activated cation channel, Piezo2, which mediates the rapidly but not intermediately or slowly adapting currents of sensory neurons. However, it remains unknown whether distinct mechanotransduction channels are sufficient for conferring specific modalities of mechanosensation. Piezo1, a homologue of Piezo2 without expression in sensory neurons, displays intermediately adapting current properties. Here we generate transgenic mice ectopically expressing Piezo1 and the associated current in sensory neurons. Remarkably, Piezo1 expression not only sensitizes light-touch in normal mice but also rescues the defective light-touch and proprioception of Piezo2 knockout mice. Intriguingly, the mechanical pain is suppressed by Piezo1 expression, but enhanced by Piezo2 deletion, suggesting its inhibition by Piezo-mediated touch sensation. Together, Piezo channels confer specific sensation of light-touch and proprioception and analgesic effect on mechanical pain. Thus, activation of Piezo2 might serve as a strategy for treating mechanical pain.

Disclosures: M. Zhang: None. **B. Xiao:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.02/GG3

Topic: D.02. Somatosensation

Support: ONR N000141512234
DOE GAANN P200A150077

Title: Limb sensory mapping: Toward a full map of the sensory innervation in larval zebrafish pectoral fins

Authors: *K. HENDERSON, M. E. HALE
Univ. of Chicago, Chicago, IL

Abstract: Larval zebrafish provide unique access to a whole, intact vertebrate nervous system in a living organism. Whole brain and spinal circuit exploration has been made possible by the optical clarity and extensive genetic toolkit available in the zebrafish. These methodological advantages can also be harnessed to explore the brain and spinal cord function in neuromechanical systems. Here we use larval zebrafish to examine the neural architecture of the pectoral fins, forelimb homologs. Previous work has described motor innervation of intrinsic pectoral fin muscles and the associated kinematics. At the larval stage, the fins beat rhythmically and have been shown to mix fluids for cutaneous respiration. Here, we investigate sensory architecture of the pectoral fin in 5 day post fertilization (dpf) larvae. We look at both Rohon-Beard neurons (RBs) and dorsal root ganglia neurons (DRGs). The RBs are an early population of mechanosensory cells considered transient and lost during the juvenile stage. We stochastically labeled RBs by injecting UAS:ptagRFP into isl2b:Gal4 embryos, imaged these at 5dpf with confocal microscopy, and reconstructed neurons and their peripheral arborizations. We found that a subpopulation of islet2B+ RBs located at the level of the fourth and fifth myomeres innervate the pectoral fin. These cells display classic RB morphology with dense primary afferent arborization. Once in the fin, the processes branch and spread through the skin. The degree of innervation of the fin varied between RBs, with some cells branching to cover a large area of the fin while others projected into smaller regions only at the base of the fin. In all cases, RBs consistently had enlargements at the ends of primary afferents within the fin. We found that the later developing DRGs also extend processes into the pectoral fins. To isolate clusters of DRGs, we photoconverted groups of cells in isl2b:Kaede fish with a 405nm laser line. At this stage, DRGs follow the path of pectoral fin motor neurons to reach the base of the fin. Within the fin, they have simpler arborizations, narrower distributions, and less elaborate endings than RBs, possibly due to the fact that these cells have not yet reached their mature morphology. Taken together, these data provide a morphological description of the sensory innervation of the 5dpf fin by two distinct cell types, one associated with early larval behaviors and one developing later and continuing to mature throughout the late larval stages. The sensory map presented here provides a basis for future functional studies of sensorimotor integration in the pectoral fin.

Disclosures: K. Henderson: None. **M.E. Hale:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.03/GG4

Topic: D.02. Somatosensation

Support: ONR Grant N000141512234
DOE GAANN Grant P200A150077

Title: Zebrafish mechanosensory afferents exhibit morphological and physiological regionalization along the body axis

Authors: *H. R. KATZ, E. MENELAOU, M. E. HALE
Univ. of Chicago, Chicago, IL

Abstract: Mechanosensory neurons play an important role in converting mechanical forces into the sense of touch. In zebrafish it is well established that Rohon-Beard (RB) neurons serve this role at the larval stage. Recent physiological studies have shown that in response to a tactile stimulus, zebrafish can produce different patterns of motor output in rostral and caudal regions of the body. There is no evidence of rostrocaudal variation in interneuron or motor neuron populations in the spinal cord that could account for these region-specific motor patterns. This led us to hypothesize that differences in the RB population between rostral and caudal regions of the body may play a role in differential axial motor output. To address this hypothesis, we examined the morphology and physiology of rostral and caudal RB populations. We used *in vivo* single cell labeling approaches in the isl2b:gal4 zebrafish to examine the architecture of their peripheral processes (n=21). We found that RB neurons exhibit morphological differences related to their somatic location. RB neurons located in rostral segments (≤15) have peripheral afferents that exit the spinal cord within one body segment of the soma (18.54um ±10.37) and their area of arborization is narrow. In contrast, RB cells located in caudal segments (>15) exit the spinal cord much further away from the soma (248.1um ±267.6) and, on average, have broader areas of arborization. We also measured the trajectory of the peripheral processes at 200um from the soma at the level of the skin across the RB neuron population (102 cells) in islt2b:GFP zebrafish. We found that more caudal RB cells tended to have more longitudinal processes that extend further caudally. To directly examine the mechanosensory response properties and receptive range of individual RB neurons, we developed a preparation for whole cell recordings while a piezo electric actuator simultaneously delivered graded mechanical stimulation at different body locations. All RB neurons examined (6 rostral; 6 caudal) exhibited fast adapting properties in response to mechanical force applied on the skin. RB neurons encoded stimulation intensity by increasing spike counts and decreasing response latency. The receptive fields established electrophysiologically matched the morphological arborization ranges: rostral cells responded to stimuli close to the soma, while caudal cells responded to more distant stimuli over a broader area. This regionalization of the zebrafish mechanosensory system can provide insights into how sensory information is encoded in the periphery and how spinal circuits transform touch information into behavioral outputs.

Disclosures: H.R. Katz: None. **E. Menelaou:** None. **M.E. Hale:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.04/GG5

Topic: D.02. Somatosensation

Support: NSF GRFP Grant DGE-1144082
NSF Grant IOS 1257886
ONR N000141512234

Title: Describing sensory innervation and texture encoding in forelimbs using a fish fin model

Authors: *A. R. HARDY, M. E. HALE
Univ. of Chicago, Chicago, IL

Abstract: Tactile sensation is critical to limb-based behaviors. Understanding limbs as touch sensors provides insight into the integration of mechanosensory information in behavior and the engineering of limb-like devices. Given the thin, optically transparent structure of fins, fish have the potential to be a complementary vertebrate model for somatosensory research to the mammalian systems currently studied. The pectoral fins, paired forelimbs of fish, function as sensors that touch and deform in response to contact with their physical surroundings. We chose the Round Goby (*Neogobius melanostomus*), a substrate associated species, to investigate 1) the ability of the fin mechanosensory system to encode the texture of contacted surfaces and 2) how mechanoreceptors are distributed throughout the fin to facilitate touch sensation. Using linear brush stimulations, we found that a subset of the afferent population has small receptive fields (~2 – 4 mm) suggestive of the ability to discriminate texture. To examine this possibility, we recorded fin ray nerve fiber activity in response to rotating 3D printed grating patterns of varying spatial period (0.5 – 7 mm) presented at a range of speeds (20 – 80 mm/sec). We found that afferents accurately encode millimeter-sized features at stimulus temporal frequencies of 3 - 50Hz, indicating similar levels of resolution to the mammalian somatosensory system and the ability to discriminate textures in their environment. We hypothesized that, similar to limb structures in other systems such as the human hand, mechanoreceptors within fins are not uniformly distributed, but instead reflect the functional demands for touch sensation. Merkel cells are an important component of touch sensation in mammals and immunolabeling has indicated their presence in fins. We sought to map the density and distribution of these putative Merkel cells across a fin. Immunolabeling with an antibody to cytokeratin 20, revealed that these cells are present and their distribution varies significantly across the fin's area. We found the highest density of putative Merkel cells in locations of fin ray branching. These regions of the fin touch, spread, and deform as fins make contact with a surface. The similar physiological responses to features of textures and apparent consistency in key sensory structures between fish

and mammals support the utility of investigating touch sensation in fins. In the applied realm, fin mechanoreceptor distribution and physiology informs optimal sensor placement for engineered sensory surfaces.

Disclosures: A.R. Hardy: None. **M.E. Hale:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.05/GG6

Topic: D.03. Somatosensation: Pain

Support: NIH grant DE018661
NIH grant DE023090

Title: Characterization of mechanoreceptors involving the sense of touch using a modified single fiber recording technique

Authors: *M. SONEKATSU, J. G. GU
Dept. of Anesthesiol. and perioperative medicine, Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: The sense of touch is transduced by highly specialized tactile-sensing organs and is important in life. A gentle touch may also produce an exaggerated painful sensation under pathological conditions. Whisker hair follicles are important tactile-sensing organs for performing tactile tasks. Although Merkel discs are one of the most prominent types of mechanoreceptors using Piezo2 channels as transducers in whisker hair follicles (Ikeda et al., Cell 2014), anatomical evidence has indicated the presence of other mechanoreceptors whose electrophysiological and functional properties are not well defined. We have previously used conventional suction recording electrode to study impulses conveyed on whisker afferent bundles following mechanical stimulation, and the responses might represent the signals from multiple mechanoreceptors. In the present study, we modified the conventional suction recording method. This allowed us to perform single fiber recordings from whisker afferent nerves to characterize electrophysiological properties of mechanoreceptors in whisker hair follicles. Using the modified single fiber recording method, we identified three types of mechanical responses following mechanical stimulation of whisker hair follicles. These three types of mechanical responses are rapidly adapting (RA) response, slowly adapting type1 (SA1) response, and slowly adapting type2 (SA2) response. RA responses had impulse firing only during rapid step of displacement stimulation. The two types of SA responses were analyzed for coefficient of variation (CoV) in their inter-spike intervals. The CoV was 0.89 ± 0.06 (n=12) in SA1 responses, consistent with the high irregularity in their inter-spike intervals. The CoV was 0.31 ± 0.02 in

SA2 responses (n=21), consistent with the high regularity in their inter-spike intervals. We investigated pharmacological properties of each type of mechanoreceptors. High concentration of serotonin (2 mM) largely inhibited SA1 responses but did not significantly affect RA responses. Similarly, Cd^{2+} a voltage-gated calcium channel blocker, also inhibited SA1 response but did not affect RA responses. Our electrophysiological and pharmacological characterization of different mechanoreceptors should help us understand physiological aspects of the sense of touch such as tactile discrimination. It may also provide insights into pathological aspects of the sense
of touch such as static and dynamic mechanical allodynia seen in pathological pain states.

Disclosures: M. Sonekatsu: 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.; DE018661, DE023090. **J.G. Gu:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH grant DE018661, NIH grant DE023090.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.06/GG7

Topic: D.04. Somatosensation: Touch

Support: Pain Relief Foundation

Title: Alterations in tactile sensation following lidocaine iontophoresis: A case of turning slow into fast?

Authors: *A. MARSHALL[1], F. P. MCGLONE[2], A. MAKDANI[2], F. O'NEILL[2]
[1]Salford Royal Hosp. Fndn. Trust, Salford, United Kingdom; [2]Liverpool John Moores Univ., Liverpool, United Kingdom

Abstract: Research objective and rationale: The role unmyelinated low-threshold mechanosensitive afferent (LTMA) fibers, C-tactile afferents (CTs), play in the expression of dynamic mechanical allodynia (DMA) is unclear. CTs fire optimally to slow gentle dynamic touch but this preferred stimulus unavoidably co-activates A-beta LTMA fibres. A method differentially blocking CTs would facilitate future human pain models assessing the role of LTMA sub-types in DMA. To address this a model utilizing non-invasive administration of lidocaine was developed. Methods: Lidocaine ($0.2mg/cm^2$) and adrenaline ($2.5\mu/cm^2$), were co-iontophoresed on a $16cm^2$ area of the volar forearm of 17 healthy participants (9 female).

Adrenaline was given to increase the depth and duration of local anesthesia. Adrenaline-only was administered contralaterally. Thermal and tactile detection thresholds as well as pleasantness and intensity ratings to slow (3cm/s) and fast (30cm/s) dynamic touch were performed bilaterally. In separate investigations the underlying neural mechanisms were explored using single unit recordings of LTMA fibres in forearm hairy skin. Assessment of mechanical threshold and firing pattern to mechanical skin stimulation were performed before and after lidocaine and adrenaline co-iontophoresis over the receptive field. Results: Compared to control, lidocaine iontophoresis resulted in significant impairment in warm ($p<0.008$), cold ($p<0.007$) and, most evidently, tactile detection thresholds ($p<0.001$). Touch pleasantness was unaffected but there was a significant reduction in intensity ratings for dynamic touch ($p<0.01$). All but one slowly adapting type 1 (SA1) fiber (6/7) showed preferential block of firing during the sustained indentation phase of mechanical skin stimulation post-lidocaine. This partial blockade temporally matched an elevation of tactile detection threshold. One slowly adapting type 2 LTMA (1/9) showed a similar pattern but other sub-types (hair follicle afferent (n=10), field unit (n=2) and CT (n=1)) showed no appreciable change in firing. Conclusions: No evidence of differential blockade of CTs following lidocaine iontophoresis was seen and the model is unlikely to be of use in deciphering their role in DMA. The lack of blockade could reflect the ion channel population, yet to be clarified, present on these fibers. Instead, the impairments to dynamic and punctate mechanical stimuli following lidocaine are associated with a phenotypic switch of SA1 fibers to fast adapting. The mechanisms underlying SA1 firing during the sustained phase of skin indentation appear more sensitive to sodium channel blockade than at onset or offset.

Disclosures: F.P. McGlone: None. **A. Makdani:** None. **F. O'Neill:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.07/GG8

Topic: D.04. Somatosensation: Touch

Support: NIAMS R01AR051219
NINDS F31NS105449
NIGMS T32GM007367

Title: Chemical neurotransmission in slowly adapting touch receptors

Authors: *B. U. HOFFMAN[1], Y. BABA[2], E. V. MOSHAROV[3], S.-H. WOO[5], D. D. ROYBAL[4], A. PATAPOUTIAN[6], D. L. SULZER[1], E. A. LUMPKIN[7]
[2]Physiol. and Cell. Biophysics, [3]Psychiatry, [4]Pharmacol., [1]Columbia Univ., New York, NY; [5]Genomics Inst. of the Novartis Res. Fndn., San Diego, CA; [6]Dept. of Neurosci., HHMI/The Scripps Res. Inst., La Jolla, CA; [7]Columbia Univ. Physicians & Surgeons, New York, NY

Abstract: As a sensory-neural organ, skin provides both a protective epithelial barrier and an environmental interface that allows organisms to react to changing conditions. Signaling between skin's epithelial cells and somatosensory neurons has recently been shown to shape touch, itch and nociception. Little is known, however, about the mechanisms through which skin cells release neuroactive molecules to govern neuronal excitability. Since their first description as "*touch cells*" in 1875, Merkel cells have served as the archetypical skin cell that mediates somatosensation. These epithelial derived cells complex with Aβ low-threshold mechanoreceptors (LTMRs) to produce slowly adapting type I (SAI) responses. Touch-sensitive Merkel cells are proposed to activate Aβ LTMRs through chemical synaptic transmission. To test this hypothesis, we employed a set of classical criteria for chemical neurotransmission as a framework. Using transcriptomic analysis, high performance liquid chromatography, and *ex vivo* electrophysiology, we show that Merkel cells are molecularly equipped for chemical synaptic transmission, and that SNARE-mediated synaptic vesicle release is required for SAI responses. Moreover, Merkel cells display robust, activity dependent release of fluorescent neurotransmitter analogues. Lastly, complementary pharmacological and genetic approaches demonstrate that Merkel-cell afferents are excited by chemical neurotransmitters, and that neuronal neurotransmitter receptors are necessary for SAI responses in Aβ LTMRs. These experiments reveal that Merkel cells form *bone fide* chemical synapses with Aβ LTMRs to encode gentle touch.

Disclosures: B.U. Hoffman: None. **Y. Baba:** None. **E.V. Mosharov:** None. **S. Woo:** None. **D.D. Roybal:** None. **A. Patapoutian:** None. **D.L. Sulzer:** None. **E.A. Lumpkin:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.08/GG9

Topic: D.04. Somatosensation: Touch

Support: NIH Grant R01NS089652

Title: What can mechanosensory neurons tell the mouse brain about whisking?

Authors: *K. S. SEVERSON[1], D. XU[1], H. YANG[2], D. H. O'CONNOR[1]
[1]Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Molecular, Cell, and Systems Biol., Univ. of California, Riverside, Riverside, CA

Abstract: Perception during active touch involves integrating information about surface features and sensor motion. We commonly interact with the tactile world using our hands, feet and orofacial regions. Despite this, our understanding of facial sensation and proprioception is limited. Classical proprioceptors are not found in most facial muscles. Instead, it is hypothesized

that low-threshold mechanoreceptors (LTMRs) could serve as “cutaneous” proprioceptors. Here, we used the mouse whisker system as a model for facial movement to investigate this hypothesis. Specifically, we surveyed cutaneous afferents at locations across the face and quantified how well they encode aspects of whisker motion.
During whisking in air, whisker afferents encode whisk phase, the relative position of the whisker within a whisk cycle. How well is whisk phase encoded by whisker afferents? And, are there other types of facial afferents that encode whisking kinematics? We compared whisking-related responses from primary afferents categorized by receptive field type: whiskers (n=67), non-mystacial vibrissae (n=35), facial fur (n=85), and jaw muscles (n=28). We used mutual information calculations to quantify how well whisk phase was encoded by each type of afferent. Jaw muscle afferents encoded the least information about whisk phase (median I = 0.42 bits/s). Facial fur afferents encoded phase (6.3 bits/s) better than jaw afferents but less well than whisker afferents (20 bits/s). Afferents with non-mystacial vibrissae receptive fields encoded phase to an intermediate degree (10 bits/s).
We next quantified how strongly movements of various parts of the face correlated with whisker motion. We found that skin motion near the whisker pad and the supraorbital and genal non-mystacial vibrissae was phase-locked with whisking. Correlated motion between these parts of the face and the whiskers explains how non-whisker afferents encode whisk phase.
In summary, whisker afferents encode whisk phase much better than other afferents. However, non-mystacial vibrissa and facial fur afferents may provide additional and complimentary proprioceptive inputs to the brain.

Disclosures: K.S. Severson: None. **D. Xu:** None. **H. Yang:** None. **D.H. O'Connor:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.09/GG10

Topic: D.04. Somatosensation: Touch

Support: NIH NINDS NS072342-01

Title: Effect of surface texture on the encoding of touch, pressure, and shear in the glabrous skin of a Rhesus macaque

Authors: *M. F. LIU[1], J. E. WINBERRY[4], C. VERSTEEG[6], T. W. SIMPSON[1], E. R. OBY[1], A. D. DEGENHART[2], A. P. BATISTA[1], R. A. GAUNT[3], S. J. BENSMAIA[5], L. E. MILLER[7], D. J. WEBER[1]
[1]Bioengineering, [2]Systems Neurosci. Inst., [3]Physical Med. and Rehabil., Univ. of Pittsburgh, Pittsburgh, PA; [4]Organismal Biol. & Anat., [5]Dept. of Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL; [6]Biomed. Engin., [7]Physiol., Northwestern Univ., Chicago, IL

Abstract: Cutaneous mechanoreceptors in the fingers encode information about the mechanics of touch, enabling the perception of grip force and object properties, such as shape, weight, and texture. Understanding the interaction between parameters such as force of contact and surface properties such as roughness, will yield insight into how the nervous system can extract object-specific information such as texture. Tactile signals originate from mechanoreceptors in the skin, innervated by nerve fibers whose cell bodies are located in the dorsal root ganglia (DRG). To elucidate how aspects of texture and touch mechanics are encoded in DRG neurons, we implanted penetrating multielectrode arrays in the C6, C7, and C8 DRG of two anesthetized rhesus macaques. We identified cutaneous and proprioceptive units via manual palpation of the arm and hand. Cutaneous units were further classified as rapidly adapting or slowly adapting based on their responses to a touch-and-hold stimulus. Tactile stimuli were delivered via two different paradigms. In the first, 10 different textured materials were scanned across the monkey's finger at fixed speeds using a rotating drum. In the second, a handheld probe was used to apply normal and shearing forces to the palm and fingers, at locations containing receptive fields for identified neurons. The probe contained a force transducer to measure the normal and shear forces. Any of several interchangeable tips was attached to the end of the probe, each containing a different material, spanning a range of roughnesses. This allowed us to examine how populations of neurons in the DRG encode contact parameters such as force and scanning speed, as well as object properties such as texture. We used the firing rates of a small population of neurons with receptive fields in the palmar surface of the hand to predict texture and speed of the stimulus with 70% accuracy. Predictions based on rapidly-adapting units were more accurate than those based on slowly-adapting units. We could also predict normal force (mean R^2 = 0.8) and shear force (mean R^2 = 0.6) from the responses of a small population of neurons with higher accuracy than from the responses of individual neurons.

Disclosures: M.F. Liu: None. **J.E. Winberry:** None. **C. Versteeg:** None. **T.W. Simpson:** None. **E.R. Oby:** None. **A.D. Degenhart:** None. **A.P. Batista:** None. **R.A. Gaunt:** None. **S.J. Bensmaia:** None. **L.E. Miller:** None. **D.J. Weber:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.10/GG11

Topic: D.02. Somatosensation

Support: Grant from Japanese Ministry of Education, Culture, Sports, Science and Technology (13780665, 14658268, 15029247, and 15300135)

Title: Effect of noradrenaline on synaptic response facilitated by peripheral mechanical stimulation by an *in vivo* patch-clamp recording

Authors: *M. SONOHATA[1], A. DOI[2], T. YASAKA[3], M. MAWATARI[1], M. YOSHIMURA[4]
[1]Saga Univ., Saga, Japan; [2]Kumamoto Hlth. Sci. Univ., KUMAMOTO, Japan; [3]Dept. Immunol., Kagoshima Univ., Kagoshima, Japan; [4]Nakamura Hosp., Fukuoka, Japan

Abstract: Introductioin: Although The substantia gelatinosa (SG) of the spinal cord is known to process not only noxious (pain) but also innocuous (touch) information, our knowledge about how these sensory inputs are moderated by exogenous noradrenaline (NA) at the synaptic level is still largely limited. In the present study, therefore, the modality selective synaptic effects of NA were investigated in SG neurons by using both in vivo anesthetized condition of rat and patch-clamp technique. **Methods:** We applied *in vivo* patch-clamp technique to anaesthetised rats to investigate the actions of NA on synaptic responses in SG neurons to mechanical stimuli before and after NA application to the surface of the L4 - L5 spinal cord. Innocuous or noxious mechanical stimuli were applied to the receptive field of the ipsilateral hindlimb with an air puff or toothed forceps, respectively. **Results:** NA reversibly suppressed the amplitude of the pinch-evoked excitatory postsynaptic currents (EPSCs) in 16 of 21 neurons (76% of control) and enhanced the amplitude in a small number of neurons. Moreover, NA inhibited the amplitude of puff-evoked EPSCs in 9 of 21 neurons (43% of control). Statistical analysis revealed that the inhibitory rate of pinch-evoked EPSCs was significantly higher than that of puff-evoked EPSCs. **Discussion:** These data indicate that NA acts on both noxious and innocuous mechanical transmission in the SG with modality specific manner. Action of NA studied *in vitro* slice preparations were only suppression of EPSCs and enhancement of IPSCs, but not enhancement of EPSCs. It is obvious that neuronal circuitry in the spinal dorsal horn in the *in vivo* preparation is completely preserved, while that in the slice preparation is very limited. Thus, the discrepancy of NA action may result from these differences.

Disclosures: M. Sonohata: None. **A. Doi:** None. **T. Yasaka:** None. **M. Mawatari:** None. **M. Yoshimura:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.11/GG12

Topic: D.04. Somatosensation: Touch

Support: NIH Grant 1R01NS101325-01A1

Title: Speed invariant coding of texture in somatosensory cortex

Authors: *J. D. LIEBER[1], K. H. LONG[2], S. J. BENSMAIA[3]
[2]ISTP/CNS, [3]Dept. of Organismal Biol. and Anat., [1]Univ. of Chicago, Chicago, IL

Abstract: We are endowed with a remarkable ability to identify objects across a wide range of contexts and perspectives. For example, we can visually identify objects over broad changes in lighting, distance, or viewing angle; we can also auditorily identify the timbre of voices and musical instruments across a wide range of loudness and pitches. In both vision and audition, perceptual invariance is achieved despite sensory representations at the periphery (the retina, the cochlea) that are highly dependent on perspective and context.
In touch, the best known instance of perceptual invariance is for texture: the tactile perception of a textured surface has been shown to be nearly independent of the speed at which it is scanned across the skin (Boundy-Singer et al., 2017). This perceptual invariance is achieved despite that fact that scanning speed strongly modulates both the firing rate and temporal patterning of responses in the somatosensory nerves (Weber et al., 2013). To achieve an invariant percept of texture, texture-specific information must be extracted from peripheral signals that are highly dependent on exploratory parameters, a process about which nothing is known.
To study these interactions, we recorded the spiking responses of neurons in somatosensory cortex - including Brodmann's areas 3b, 1, and 2 - to natural textures scanned over the skin at various speeds, spanning the range used in natural texture exploration. We then compare the effect of speed in cortical responses to their peripheral counterparts. We find that, while the strength of the response evoked by textures in tactile fibers is highly speed-dependent, the strength of the response of many neurons in somatosensory cortex is speed-independent. This speed independence gives rise to a rate-based texture representation in cortex which, unlike its counterpart in the nerve, is robust to changes in scanning speed. We also find that a subset of neurons in cortex exhibit responses to texture that are temporally patterned, much like those in the periphery, and that these patterns scale with speed. As the rate-based code is sufficient to account for our ability to perceive textures across changes in scanning speed, however, the role of these temporal signals in cortex remain to be elucidated.

Disclosures: J.D. Lieber: None. **K.H. Long:** None. **S.J. Bensmaia:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.12/GG13

Topic: D.04. Somatosensation: Touch

Support: ESA (European Space Agency), Prodex, IAP VII/19 DYSCO (BELSPO, Belgian Federal Government)
EU-FP7 Marie Curie Initial Training Network PROTO-TOUCH (Grant Agreement no. 317100)

Title: Fingertip skin deformation during the pre-loading phase of lifting

Authors: *F. SCHILTZ[1], A. BARREA[2], J.-L. THONNARD[3], P. LEFEVRE[4]
[1]Catholic Univ. of Louvain, Louvain la Neuve, Belgium; [2]Univ. Catholique de Louvain, Louvain-la-Neuve, Belgium; [3]Univ. Catholique de Louvain, Brussels, Belgium; [4]ICTEAM and Inst. of Neuroscience, Univ. Catholique de Louvain, Louvain-la-Neuve, Belgium

Abstract: The specific friction between fingertip and object has been shown to affect the coordination of finger forces during the early phases of object lifting. We hypothesize that the effect of friction on finger forces is mediated by fingertip deformation. Here, we investigated the relationship between object friction and fingertip deformation and how the latter affects the control of finger forces. To this end, we designed a compact instrumented object equipped with a camera allowing recording the fingertip skin deformation during manipulation. The object was designed to be held in precision grip, i.e. between the thumb and index finger. In addition, it is equipped with sensors measuring forces and torques applied by the thumb and index finger on the object. In the experiment, a human subject was asked to grasp the manipulandum in precision grip, lift it approximately 10cm above its support, hold it for a few seconds, and then place it back on the support. This procedure was repeated twenty times in consecutive trials. The proportion of the contact area between fingertip and object that experienced slipping was determined using image processing techniques. First, feature points were sampled automatically within the contact area. Then, the position of these points was tracked across consecutive frames using an optical flow algorithm. A point was considered slipping if it moved more than a fixed threshold between two consecutive frames. Two frictional conditions were tested. In the first one, the subject manipulated the object with bare fingers, while in the second condition fingertips were coated with oil. Analysis of the sticking and slipping parts of the contact area showed that the sticking part propagated from the center to the periphery of the contact during the preloading phase. Further analysis showed that fingertip skin underwent large mechanical deformation under the oil condition during the pre-loading phase, i.e. during the built-up of grip force before the object is lifted off the table. This suggests that skin deformation during the pre-loading phase may constitute valuable information about friction between fingertip and object that could be transmitted by the mechanoreceptors of the fingertips to the central nervous system in the very first stages of lifting.

Disclosures: F. Schiltz: None. **A. Barrea:** None. **J. Thonnard:** None. **P. Lefevre:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.13/GG14

Topic: D.04. Somatosensation: Touch

Support: NSF Grant IIS-1320635

NSF Grant DMS-1436591

Title: A quantitative perceptual model for tactile roughness

Authors: *C. TYMMS[1], E. P. GARDNER[2], D. ZORIN[1]
[1]Computer Sci., New York Univ., New York, NY; [2]Dept Physiology/Neuroscience, New York Univ. Sch. of Med., New York, NY

Abstract: Everyone uses the sense of touch to explore the world, and roughness is one of the most important qualities in tactile perception. Roughness is a major identifier for judgments of material composition, comfort and friction, and it is tied closely to manual dexterity. The advent of high-resolution 3D printing technology provides the ability to fabricate arbitrary 3D textures with surface geometry that confers haptic properties. In this work, we address the problem of mapping object geometry to tactile roughness. We fabricate a set of carefully designed stimuli and use them in experiments with human subjects to build a perceptual space for roughness. We then match this space to a quantitative model obtained from strain fields derived from elasticity simulations of the human skin contacting the texture geometry, drawing from past research in neuroscience and psychophysics. We demonstrate how this model can be applied to predict and alter surface roughness, and we show several applications in the context of fabrication.

Disclosures: C. Tymms: None. **E.P. Gardner:** None. **D. Zorin:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.14/GG15

Topic: D.04. Somatosensation: Touch

Support: NIH/ NICHD Grant 1R01HD071978-01A1

Title: Adaptation of fingertip forces to 3D printed surfaces and loads during grasp and lift

Authors: *P. RAGHAVAN[1], S. BILALOGLU[2], C. TYMMS[4], M. CAUGHEY[7], J. STONE[2], A. SHALABI[5], R. NARASIMHAN[8], Y. LU[9], D. ZORIN[6], E. P. GARDNER[3]
[1]Rehabil. Med., New York Univ. Langone Med. Ctr., New York, NY; [3]Dept Physiology/Neuroscience, [2]New York Univ. Sch. of Med., New York, NY; [4]Computer Sci., [6]Dept. of Computer Sci., [5]New York Univ., New York, NY; [7]NYIT Col. of Osteo. Med., Long Island, NY; [8]Cornell Univ., Ithaca, NY; [9]Dept. of Applied Statistics, Social Sci. and Humanities, NYU Steinhardt, New York, NY

Abstract: Grasping an object requires intricate coordination of tactile perception with fine motor skills. In particular, humans adapt fingertip grip forces to the object's surface friction and adapt

their load forces to the object's weight. If the adjustment in grip-load force is too small, the object may be dropped, while applying too much force, risks damaging it. Some attention has been given to perception of surface friction in the past, but it has typically focused on non-controllable natural materials or on a narrow range of artificial materials. The advent of high-resolution 3D printing technology provides the ability to fabricate arbitrary 3D shapes with textures of precise surface geometry to be used in tactile studies. Using high resolution stereolithography 3D printing and parametric modeling, we created eight different textures, whose texture elements were small bumps with diameters of 0.1, 0.3, or 0.5 mm, and had a mean spacing of 0.75 mm, 1.0mm, or 1.25mm. Previous studies demonstrated that surfaces with small wavelengths and large textons were judged most smooth, and textures with large wavelengths and small textons were judged least smooth. We used these same surfaces to measure the interaction between surface texture and object mass on efficient grasp-and-lift actions. Ten healthy adult subjects grasped and lifted an instrumented grip device with 3D printed surfaces and weights of 250, 450 and 650 g. The adaptation of fingertip forces was quantified using the peak grip force rate (PGFR) and grip force at lift (GF). We quantified the coefficient of friction (COF) as the inverse of the slip ratio (grip force/ load force at the moment of slip). We found that the load lifted had clear effects on grip force, but the texture effects were weaker due to a small range tested. Rough surfaces with large spacing and small diameter textons result in a significantly higher COF and produced lower PGFR. Friction was negatively correlated with subjective smoothness estimates. Textures generated with different texton size and spacing using stereolithography 3D printing can be used to generate a variety of quantified frictional surfaces that then can be used in studies for tactile roughness perception and in related neurological applications.

Disclosures: P. Raghavan: None. **S. Bilaloglu:** None. **C. Tymms:** None. **M. Caughey:** None. **J. Stone:** None. **A. Shalabi:** None. **R. Narasimhan:** None. **Y. Lu:** None. **D. Zorin:** None. **E.P. Gardner:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.15/GG16

Topic: D.04. Somatosensation: Touch

Support: NIH/NIBIB (P41-EB018783)
NIH/NICHD (R25-HD088157)
NIH/NIMH (P50-MH109429)
US Army Research Office (W911NF-14-1-0440)
Natural Science Foundation and Major Basic Research Program of Shanghai (16JC1420100)

National Natural Science Foundation of China (51620105002).
Shanghai Sailing Program (18YK1403300)

Title: Localizing sensorimotor cortex using vibro-tactile stimulation

Authors: *T. XIE[1,2], Z. WU[3], P. BRUNNER[1,4], X. SHENG[2], X. ZHU[2], G. SCHALK[1,4,5], L. CHEN[3]
[1]Nat. Ctr. for Adapt. Neurotechnologies, Wadsworth Ctr., New York State Dept. of Hlth., Albany, NY; [2]State Key Lab. of Mechanical Syst. and Vibration, Shanghai Jiao Tong Univ., Shanghai, China; [3]Dept. of Neurosurg., Huashan Hospital, Fudan Univ., Shanghai, China; [4]Dept. of Neurol., Albany Med. Col., Albany, NY; [5]Dept. of Biomed. Sci., State Univ. of New York, Albany, NY

Abstract: Localization of sensorimotor cortex is often performed during presurgical planning prior to resective brain surgery to minimize post-surgical deficits. Electrical stimulation of the median nerve (MNS) has been used for decades to identify the central sulcus, i.e., the boundary between motor and sensory areas. MNS is typically performed by qualitatively assessing the polarity and shape of the responses to electrical stimulation, which has to be done by experts and can lead to ambiguous results. We aim to overcome these limitations by developing an alternative technique that is quantitative (and hence can be automated) and accurate. In our ongoing study, we localized sensorimotor cortex by assessing population-level cortical responses to vibro-tactile stimulation and compared the results to those obtained by median nerve stimulation and self-paced movement.
To date, we collected data from two human subjects who underwent an awake craniotomy and median nerve stimulation for the purpose of localizing sensorimotor cortex prior to tumor resection. Both subjects had electrocorticographic (ECoG) grids placed over sensorimotor cortex (8x8 configuration, 5mm inter-electrode spacing, 2mm exposed diameter). While the subjects were awake during the surgery, we performed three experiments on the hand contralateral to the implant while acquiring ECoG signals at 2048 Hz: (1) Median nerve stimulation of the wrist for a duration of 1-6 minutes (2.3 Hz, bi-phasic, 5.5-7.5mA current); (2) Vibro-tactile stimulation of the index finger for a duration of 10 minutes (175 Hz vibration frequency, pulsed at 23-29 Hz); (3) Self-paced flexion of the index finger (40-60 trials of 2s flexion and 3-4s rest). In offline analyses, we determined the spatial concordance between the functional maps of sensorimotor cortex determined by analysis of ECoG broadband gamma (60-140 Hz) activity during vibro-tactile stimulation and finger movement, and their relationship to the location of the central sulcus as determined from median nerve stimulation.
Our results show that vibro-tactile stimulation and self-paced finger flexion produce broadband gamma responses anteriorly and posteriorly to the central sulcus and that these responses have distinct time courses that may be informative for attributing them to motor or sensory cortex. Furthermore, vibro-tactile stimulation activates a subset of the cortical areas that are activated by self-paced finger movement. With additional data, our study may lead to a new clinical procedure for automatic localization of sensorimotor cortex.

Disclosures: T. Xie: None. **Z. Wu:** None. **P. Brunner:** None. **X. Sheng:** None. **X. Zhu:** None. **G. Schalk:** None. **L. Chen:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.16/GG17

Topic: D.04. Somatosensation: Touch

Support: NSERC Grant 400723

Title: The effects of remote subthreshold electrical stimulation on skin sensitivity in the lower extremity

Authors: *E. PLATER[1], R. PETERS[2], L. BENT[1]
[1]Univ. of Guelph, Guelph, ON, Canada; [2]Univ. of Calgary, Calgary, ON, Canada

Abstract: Introduction: Skin at the foot sole acts as an interface with the support surface and can therefore affect balance. Lower extremity amputation (LEA) leads to changes in the skin interface. The skin at the foot sole is glabrous; in LEA, the interface between the residual limb and the prosthetic socket is comprised of hairy skin, which has different sensory properties, the specifics of which are not as well known. A sensory augmentation technique, stochastic resonance (SR), has been shown to improve sensitivity in glabrous skin through application of a remote subthreshold stimulus. The objective of the current study was to determine if remote subthreshold electrical stimulation at the foot sole and hairy skin on the posterior leg can improve sensation to a vibration stimulus in a similar way, in healthy individuals with no sensory impairments.
Methods: 10 young, healthy subjects (5 females, age 22-27 years) had a vibrotactile stimulus applied to the second metatarsal, heel and calf at the same time that an electrotactile noisy stimulus was applied remotely to the posterior calf (for second metatarsal and heel locations) or thigh (for calf location). Thresholds were determined for both stimuli (vibro or electrotactile) prior to testing. A two forced-choice protocol was then used to determine detection ability of the vibration at 90% of determined threshold, with varying electrotactile levels superimposed. A greater percent-correct value indicated better detection. Any value above 67.5% correct was considered significantly above a guessing rate and was determined to be an “SR effect”.
Results: 30 observations were compared (10 subjects x 3 skin sites). Of these, approximately half (13/30) showed an SR effect. When present, the SR effect did not have a clear distribution across noise intensities. On average, the SR effect was larger at the calf (0.53) than the other sites (0.15, 0.38) There is some evidence of a relationship between performance on two different sites in a single individual.
Discussion: The SR effect was seen here in both glabrous and hairy skin in a subset of the observations. Previous studies suggest that there is an optimal noise intensity that most effectively improves sensitivity; this was seen here but it appears to vary between individuals

and sites. Our results suggest that subthreshold electrotactile stimulation may be effective at improving skin sensitivity to vibration on both glabrous and hairy skin, but the intensity required varies between individuals and locations and is not effective in everyone. Testing in an LEA population is the next step with future work targeting new technology in prosthetics to improve balance and prevent falls.

Disclosures: E. Plater: None. **R. Peters:** None. **L. Bent:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.17/HH1

Topic: D.04. Somatosensation: Touch

Title: Study on brain imaging when using micro-cone to reduce pain using fmri

Authors: *S. FUKASAWA[1,3], H. EDA[2], S. IDE[3]
[1]Grad. Sch. for GPI, Nishi-Ku Hamamatsu, Japan; [2]Grad. Sch. for GPI, NIshi-ku Hamamatsu, Japan; [3]ToyoResin, Shizuoka, Japan

Abstract: Introduction Due to its response with diverse factors, pain mechanism has not been elucidated. Instead, importance of pain management has been pointed out. We made a report on SfN in 2013. Pain is relieved by attaching a micro-cone. Objective of the study is to examine fMRI images during pain relief. Methods Applying pain stimulus in the experiment, a comparison was performed between those with and without pain relief effect. We designed a factor-based experiment using two factors (2×2 levels). A stick (ToyoResin corporation, Japan) was used to relieve pain. Somacept•Somareson (ToyoResin corporation, Japan) was used as micro-cone disk for pain relief. A flat disc was used as placebo with no pain relief by removing micro-cone projections. MAGNETOM Verio (3T) made by Siemens was used for fMRI. Pressure stimulus was given on the side of little finger nail. Prior to stimulation, a disc was attached between PM and CM joints on the back of the hand. The experiment was performed by replacing attached micro-cone and placebo twice separately by new one. The subject was a healthy woman aged 45. All procedures were approved by Ethics and Study Committees of ATR-Promotions, Inc (ATR Ethics Committee, Ethical number 13-020). Result The subject was asked in advance about degree of pain when stimulus was given. Evaluation was based on VAS value. It was 7 against 10 as the maximum unbearable pain. The figure shows images when the same pain stimulus was given under conditions with (Fig. 2) and without (Fig.1) micro-cone. condition. A pain stimulus image without micro-cone showed activities on multiple sites in the brain. ($p < 0.01$) Such activity was not observed in a pain stimulus image with micro-cone. Conclusion Reported VAS value indicates that the subject felt pain by the stimulus. The image without micro-cone showed a state of the brain feeling a pain. The result was coincident with

previous knowledge on PainMatrix. Activities were observed on multiple sites in the brain. Regarding PainMatrix, we referred to Plant 73 (1997) 431-445 published by Derbyshire et al. in 1997. Activities were observed at S1, S2, insula, ACC, and thalamus in placebo. An image has suggested that activities were not recognized at such sites (e.g. S1, S2, insula, ACC, thalamus) even feeling the same pain stimulus by attaching a micro-cone.Micro-cone has suggested its mechanism to suppress activities at sites feeling a pain. The current experiment has provided just a preliminary result of one subject.In order to clarify brain activity when a pain is relieved by a micro-cone, we intend to examine the mechanism by further increasing subjects in the future.

Disclosures: S. Fukasawa: None. **H. Eda:** None. **S. Ide:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.18/HH2

Topic: D.04. Somatosensation: Touch

Support: Rowley Grant, University of Chicago
NIH F31NS096952

Title: Characterizing breast sensation and its relationship with sexual arousal

Authors: K. H. LONG[1], A. K. SURESH[1], *S. J. BENSMAIA[2]
[1]Committee on Computat. Neurosci., [2]Dept. of Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: Each year, 100,000 women undergo mastectomy, including a growing number who elect bilateral prophylactic mastectomy to reduce their risk of breast cancer. Most (40-80%) of the women who have this procedure experience loss of sexual function, even among the majority who are satisfied with the appearance of their reconstructed breast(s). Surgical innovations have led to marked advances in restoring the breast's physical *form*, but very little has been done to restore or preserve breast *function*, including touch (discriminative, affective, and erogenous), thermoreception, and thermoregulation. As is well-understood for the role of penile function in male sexual physiology, these sensorimotor and neurovascular components of breast function are essential to normal female sexual physiology. Simple (or total) mastectomy, the most common mastectomy procedure for women with breast cancer, amputates all of the breast tissue, including the lateral cutaneous branches of the third through sixth intercostal nerves and the entire nipple areolar complex (NAC), preserving the underlying pectoral muscles and axillary lymph nodes. This loss of innervation causes partial or complete loss of sensation in the breast. To develop strategies for preserving and restoring breast function, we aim to identify (1) the contribution of specific mechanoreceptive afferents in both the breast and the NAC, (2) the role

of individual intercostal nerves in breast sensation and arousal, and (3) the relationship between arousal and breast sensation. To this end, we designed and constructed an experimental apparatus to passively deliver diverse, well-controlled tactile stimuli to the breast and NAC. With this apparatus, we present a variety of tactile stimuli - including vibrations and textures - and have subjects perform perceptual judgments adapted from well-established psychophysical paradigms. We then use virtual reality audiovisual stimuli to elicit a state of sexual arousal and investigate the effects of arousal on breast sensation. Finally, we pharmacologically block individual intercostal nerve fibers and assess the impact on sensation and arousal.

Disclosures: K.H. Long: None. **A.K. Suresh:** None. **S.J. Bensmaia:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.19/HH3

Topic: D.04. Somatosensation: Touch

Support: NSERC Grant 400723

Title: Sensitivity of foot cutaneous mechanoreceptors is altered by ankle-joint posture

Authors: *S. G. SMIITH[1], S. BEAUDETTE[1], S. BROWN[1], L. BENT[2]
[1]Univ. of Guelph, Guelph, ON, Canada; [2]Univ. Guelph, Guelph, ON, Canada

Abstract: Background:
Locomotor patterns are adapted to account for changes in our environment. Modification of such patterns are achieved through sensory inputs, for which cutaneous feedback from the foot is known to have a crucial role. The foot moves through various postures with locomotion, which results in structural deformations to the skin of this region. It is important to assess if skin sensitivity, and therefore contribution, is modified in different foot postures along with structural deformations.
Aim: To assess the effect of ankle posture on skin sensitivity measures across the foot.
Methods: 20 subjects (9 male, age = 22 ± 1) were positioned with their right foot in dorsiflexion, plantarflexion, and a neutral posture. Measures of perceptual skin sensitivity were assessed across the foot sole or dorsum; proximal, middle, or distal regions of the dorsum or the heel, medial arch, lateral arch, and the first metatarsal of the sole. Tactile sensitivity tests were used to target subclasses of cutaneous mechanoreceptors and included measures of touch contact sensitivity (Semmes Weinstein monofilaments for FAI), stretch sensitivity (fastened tabs, SAII), and spatial acuity (JVP Domes, SAI.)
Results:
Sensitivity differed significantly across locations; increased sensitivity to touch contact at the

distal site and medial arch as well as decreased sensitivity at the heel and proximal site. Skin stretch and spatial acuity measures were most sensitive at the heel. For posture, skin sensitivity was altered at regions that undergo large structural deformations, such as the foot dorsum and metatarsals, across ankle postures. Specifically, skin stretch resulted in decreased monofilament sensitivity on the foot dorsum as well as increased sensitivity to longitudinal stretch. Sensitivity to transverse stretch also increased across the foot dorsum. The opposite response occurred with skin retraction. Spatial acuity was not altered by postures.
Conclusions: Skin sensitivity was found to be location dependent on the foot sole and dorsum for almost all measures, with the heel being most sensitive for skin stretch and spatial acuity and the medial arch being the most sensitive for touch contact. Overall, touch contact sensitivity was decreased with skin stretch and increased with retraction. The opposite occurred with stretch; with greater sensitivity in a stretched position. As a result we suggest the structural alterations to the skin on the foot across postures affects skin sensitivity.
Significance: The ability of skin input to alter gait outcomes may be variable across ankle postures, which changes the effectiveness of interventions across phases of movement.

Disclosures: S.G. Smiith: None. **S. Beaudette:** None. **S. Brown:** None. **L. Bent:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.20/HH4

Topic: D.02. Somatosensation

Title: Direct effects of simulated knee movements on firing behavior of muscle spindles located within a one-joint ankle extensor

Authors: *H. MAAS, W. NOORT
Dept. of Human Movement Sci., Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: We recently showed in rat that muscle spindles not only signal length changes of the muscle in which they are located, but also local length changes that occur as a result of changing the length of synergistic muscles (Smilde et al. J. Neurophys. 2016). The mechanism for this is force transmission via connective tissue linkages between adjacent muscles. However, in our previous study, the imposed relative muscle positions were non-physiological, i.e. only one of the triceps surae muscles (e.g. soleus, SO) was lengthened distally. The aim of the present study was to investigate the effects of intermuscular connections on feedback from muscle receptors during physiological conditions. We hypothesized that proximal length changes of the two-joint ankle plantar flexors (mimicking knee extension) will affect the output from muscle spindles located with the one-joint SO. In fully anesthetized Wistar rats (n=20), the distal tendons of SO, lateral gastrocnemius (LG) and plantaris (PL) were dissected, cut and together tied to a servo

motor, which controlled MTU length and measured tendon force. Also the shared proximal tendon of LG and PL was attached to a servo motor. Connective tissues at the muscle belly level were left intact. Action potentials from single afferents were recorded intra-axonally by penetrating dorsal roots. Axons from muscle spindles were identified using their characteristic response properties. To assess in which muscle the spindle was located, the muscle surface was probed. To further confirm location within SO, ramp stretches were applied both distally (including SO) and proximally (only including LG and PL). Afferent firing was measured during distally applied 3 mm ramp stretches (20 mm/s), corresponding to ankle plantar flexion from 90° to 45°. During the hold phase, three successive proximally applied symmetric triangular stretch-release trials (1 mm, 2mm/s; corresponding to knee extension from 90° to 110°) were performed. Instantaneous firing rate (IFR) was instantly affected by LG+PL triangular stretch-releases in 20 out of 27 SO muscle spindles. Not lengthening, but shortening of LG+PL proximally resulted in an increase of the IFR, by on average 26 pulses per second). These results extend previous findings that output of muscle spindles can be affected by length changes of neighboring muscles, also if conditions stay within physiological limits. This indicates that spindles do not encode angles of individual joints unambiguously, but may also provide information about adjacent joints that the muscle does not span and, hence, limb endpoint position.

Disclosures: H. Maas: None. **W. Noort:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.21/HH5

Topic: D.02. Somatosensation

Title: Neural substrates of a proprioceptive discrimination task

Authors: *N. ELANGOVAN[1], A. MAHNAN[2], J. KONCZAK[3]
[1]Sch. of Kinesiology, [3]Human Sensorimotor Control Lab., [2]Univ. of Minnesota, Minneapolis, MN

Abstract: Proprioceptive inputs from the limbs are crucial for producing accurate movements. Impairment in proprioception leads to movement deficits in neurological conditions. Proprioceptive evaluation typically involve a position sense discrimination task. However, the cortical areas involved in the processing proprioceptive discrimination task has never been systematically evaluated. Here, we evaluate a neural substrates of a wrist position sense discrimination task using electroencephalography (EEG). Healthy adults with no known neurological deficits were recruited for study participation. Testing involved 2 steps - threshold estimation and EEG evaluation. Proprioceptive discrimination thresholds were determined using a 2-alternate forced choice paradigm. Each participant discriminated wrist position stimuli for 30

trials, verbally identifying the farthest position among stimulus pairs in each trial. A wrist robotic apparatus was used to deliver the position sense stimuli. Size differences between the position sense stimulus pairs were obtained by psi-marginal method, an adaptive psychophysical algorithm. Thresholds were estimated based on subject responses and stimulus size differences using a logistic-weibull function. After threshold estimation, each participant completed 300 discrimination trials with a supramaximal stimulus (150% of threshold) under EEG. Instruction on whether to identify the nearest or the farthest position was randomized during the discrimination trials. Participants were cued on the decision after the stimulus pairs were presented. This delayed cue was introduced during EEG evaluation to dissociate the processes related to proprioceptive discrimination from verbal judgment. We present the results of event-related activity during the proprioceptive discrimination task in the frontal and parietal cortical areas. These results provide insights on the influence of proprioceptive processing in the perceptual and the motor areas and thereby cortical motor processing.

Disclosures: N. Elangovan: None. **A. Mahnan:** None. **J. Konczak:** None.

Poster

668. Touch and Proprioception

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 668.22/HH6

Topic: D.02. Somatosensation

Support: NIH NIAMS Grant R01-AR050520
NIH NIAMS Grant R01-AR052345
US DoD CDMRP Grant MR150091

Title: An integrative neuromorphic approach to modeling of voluntary motor function

Authors: *S. CHAKRAVARTHI RAJA[1], F. J. VALERO-CUEVAS[1,2,3]
[1]Dept. of Electrical Engin., [2]Dept. of Biomed. Engin., [3]Div. of Biokinesiology and Physical Therapy, USC, Los Angeles, CA

Abstract: In Niu, et al. (2017) we implemented a realtime Field-Programmable Gate Array (FPGA)-based simulation of neuromorphic models of monosynaptic stretch reflex circuitry of an agonist-antagonist muscle-pair. We then characterized the system in Jalaleddini, et al. (2017) by coupling the simulation to the flexor digitorum profundus and the extensor carpi radialis longus tendons of the MCP joint of a cadaveric hand preparation to show that such systems can indeed evoke human-like stretch reflexes as in the work of Edin and Vallbo (1990).
We now present improvements to that system such as including Golgi tendon organs, Renshaw cells, and polysynaptic interneuronal pathways to form a system akin to a simplified spinal-like regulator as in Raphael et al. (2010). Nonlinear adaptive controls and simple neural networks

allow us tune the descending commands (pulse trains) to both fusimotor and alpha motoneuron pools. We use such time-based running of descending commands to demonstrate the ability to produce “voluntary” movement. We find that realistic models of muscle mechanics, force-velocity properties in particular, are critical to produce stable movements. By selectively adding/removing components and interconnections, we are also able to show the sufficiency of the same for enabling voluntary movement. Future extensions will include homonymous and heteronymous sensorimotor pathways to control more muscles and produce motor function in cadaveric human fingers.

The authors acknowledge Dr. Gerald E. Loeb, Dr. Terence D. Sanger and Dr. Kian Jalaleddini for their guidance with the setup of the system.

The research reported in this work is partially funded by National Institutes of Health grants *NIAMS R01-AR050520* and *NIAMS R01-AR052345*, and US Department of Defense CDMRP grant *MR150091* awarded to Dr. Francisco J. Valero-Cuevas. The content of this endeavor is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the US Department of Defense.

Disclosures: S. Chakravarthi Raja: None. **F.J. Valero-Cuevas:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.01/HH7

Topic: D.07. Vision

Support: CIHR

Title: Pulvinar modulates contrast responses in visual cortex as a function of cortical hierarchy

Authors: *N. CORTES[1], B. O. SOUZA[2], C. F. CASANOVA[3]
[1]Ecole d'optometrie, Univ. De Montreal, Montreal, QC, Canada; [2]École d'Optométrie, École D'Optométrie, Univ. De Montréal, Montreal, QC, Canada; [3]Univ. Montreal, Montreal, QC, Canada

Abstract: The pulvinar is the main extrageniculate visual nucleus in all mammals including humans. Given its extensive reciprocal connectivity with the visual cortex, it allows the transthalamic cortico-cortical transfer of visual information. Little is known about the driver or modulatory nature of these connections across the visual hierarchy. To address this question, we studied the impact of pulvinar inactivation on the contrast response function (CRF) of neurons localized in two distant hierarchical levels of the cat visual cortex: areas 17 and 21a. Single-unit responses to gratings presented at different contrasts were recorded in both areas using linear probes before, during and after the GABA inactivation of the lateral (LPl) or medial (LPm) parts

of the lateral posterior nucleus. Here, the distinction between driver (D) and modulator (M) inputs was based on its effects on the CRF. Linear effects (e.g., changes of CRF position; C50) were associated with D inputs, while nonlinear effects (e.g., changes of CRF dynamic range; Rmax) with M inputs (Abbot and Chance, 2005). In area 17, LPl inactivation impacted mostly the Rmax with 63% of cells showing an increased and 37% a decrease of activity. Only 3 cells showed an increase of C50. Moreover, putative excitatory neurons (i.e., regular spiking cells) showed most of the Rmax changes, with supra- and infragranular layers presenting increased and decreased activity, respectively. In area 21a, LPl inactivation yielded an increase in Rmax for most cells (30/35) irrespective of the excitatory/inhibitory nature, with only 2 neurons exhibiting changes in C50. The inactivation of the LPm yielded an increase in C50 and Rmax for 1/3 of 21a cells (11/31), while for the rest, only the Rmax increased. These effects were not layer- nor cell-type dependent. Overall, the impact of the pulvinar inactivation was stronger in area 21a than in area 17. In addition, while the pulvinar inactivation caused changes in Rmax in area 17, it led to changes to both Rmax and C50 in area 21a. Thus, these findings indicate that the pulvino-cortical signals are mostly modulatory in area 17 and modulatory and driver in area 21a. The distinctive influence of pulvinar across the cortical hierarchy may play a central role in visual attention mechanisms.

Disclosures: N. Cortes: None. **B.O. Souza:** None. **C.F. Casanova:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.02/HH8

Topic: D.07. Vision

Support: Whitehall Foundation Research Grant
NIH R01 EY25219
Albert J Ryan Foundation

Title: Corticogeniculate feedback enhances suppression of extraclassical surround in select LGN neuron subtypes

Authors: *A. J. MURPHY[1,2,3,4,5], J. M. HASSE[5,3,4,7], F. BRIGGS[5,3,4,6]
[1]Rochester, NY; [2]Neurosci. Grad. Program, [3]Ernest J. Del Monte Inst. for Neurosci., [4]Ctr. for Visual Sci., [5]Neurosci., [6]Brain and Cognitive Sci., Univ. of Rochester, Rochester, NY; [7]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: An important function of the visual system is to filter relevant visual information from the noisy visual environment. The corticogeniculate (CG) pathway, which connects primary visual cortex (V1) with the visual thalamus (lateral geniculate nucleus or LGN) in the feedback

direction, may play a role in this filtering process. Previous work has shown CG feedback results in LGN gain modulation, changes in LGN spiking mode, timing, and precision, and sharpening of LGN receptive fields. How CG feedback modulates the extraclassical surround of LGN neurons remains unresolved. We address the contribution of CG feedback to extraclassical surround suppression of LGN neurons by optogenetically manipulating CG feedback neurons in areas 17 and 18 of anesthetized ferrets. First, we inject a modified Rabies virus expressing m-Cherry and channelrhodopsin2 (ChR2) into the LGN such that CG neurons are selectively infected. Following surgical virus injection, we perform an in vivo experiment in which we place electrode arrays into retinotopically-aligned regions of the LGN and V1. We use a fiber-optic cable to deliver 465nm LED light that activates ChR2-expressing CG neurons in the visual cortex. We record the activity of V1 and LGN neurons in response to drifting sinusoidal gratings and m-sequence stimuli under conditions in which CG neurons expressing ChR2 are light-activated. Preliminary results of m-sequence stimulation suggest that the total extent of extraclassical surrounds among LGN neurons are slightly reduced with optogenetic activation of CG feedback. Additionally, optogenetic activation of CG feedback differentially modulates surround suppression among LGN neurons dependent upon size tuning. Together these results suggest CG feedback influences LGN extraclassical surrounds in a cell type specific manner.

Disclosures: A.J. Murphy: None. **J.M. Hasse:** None. **F. Briggs:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.03/HH9

Topic: D.07. Vision

Title: Retinotopic mapping of the optic radiation tract

Authors: *O. ABDULLAH[1], K. DESIMONE[2], A. TEMUDO[3], K. SREENIVASAN[3]
[1]Abu Dhabi, United Arab Emirates; [2]Psychology, New York Univ., New York City, NY; [3]Psychology, New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates

Abstract: A central aim of cognitive and clinical neuroscience is to map structure to function, which will enable the prediction of functional deficits from structural damage. In clinical practice, evidence from post neurosurgical evaluations has underscored the importance of minimizing damage to white matter structures in the brain during tumor resections. For example, damage to the optic radiation (OR) tract can result in serious visual field defects. The OR carries visual field information from the lateral geniculate nucleus (LGN) to primary visual cortex (V1). An important gap in our knowledge is understanding the relationship between individual fiber bundles within the OR and information about specific parts of the visual field.
Diffusion-MRI (dMRI) has emerged as a noninvasive modality for tracing and virtually

dissecting major white matter bundles in the living brain. Several studies highlighted the utility of dMRI for predicting post-surgical damage of the OR in individual patients. However, due to variability of the location and trajectory of the OR between subjects, this technology has not been widely adopted. In this study, we combined retinotopic mapping of the visual cortex obtained from functional magnetic resonance imaging (fMRI) to guide dMRI fiber tracking algorithms of the OR in young healthy male and female adults. We analyzed data from the publicly available Human Connectome Project dataset (10 subjects; 7T fMRI co-registered to 3T and 7T dMRI), as well as data that we acquired at New York University Abu Dhabi (4 subjects; 3T fMRI co-registered to 3T dMRI). The fMRI data was collected during visual stimulation with high contrast sweeping bar and expanding ring stimuli. We employed a population receptive field (pRF) approach, which assigned each voxel a receptive field center and size. The aggregate maps were used to draw visual regions of interest and determine polar angle and eccentricity maps, consistent with standard retinopic mapping procedures. The fMRI-generated maps in V1 were used in turn to classify specific white matter bundles in the OR (LGN to V1) according to their terminating points in V1, which provided white matter retinotopic dissection of the visual field. Eccentricity color-coded OR resembled a ribbon-like structure entering V1 with the foveal fibers occupying the middle part. When color-coded with the Polar Angle, the OR where mainly split into superior and inferior parts resembling the lower and upper visual fields. The combination of fMRI and dMRI to assign specific functional roles to white matter tracts represents a potentially valuable tool both for basic science and as a guide for neurosurgeries conducted under general anesthesia.

Disclosures: O. Abdullah: None. **K. DeSimone:** None. **A. Temudo:** None. **K. Sreenivasan:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.04/HH10

Topic: D.07. Vision

Support: DFG BU 1808/5-1
SFB 870 TPB19

Title: Visual response properties of mouse TRN are consistent with its potential role for feedback-mediated surround suppression

Authors: *G. BORN[1,2], M. A. SPACEK[1], C. LAO[3], L. BUSSE[1,4]
[1]Div. of Neurobiology, Dept. Biol. II, LMU Munich, Planegg-Martinsried, Germany; [2]Grad. Sch. for Systemic Neurosciences, LMU Munich, Planegg-Martinsried, Germany; [3]Inst. of

Physiological Genomics, Viral Vector Facility, LMU Munich, Planegg-Martinsried, Germany; [4]Bernstein Ctr. for Computat. Neurosci. Munich, Planegg-Martinsried, Germany

Abstract: Neurons in the dorsolateral geniculate nucleus (dLGN) of the thalamus are suppressed by stimuli extending beyond the classical receptive field into the surround. Surround suppression increases between the retinal ganglion cells and dLGN, where it has been hypothesized that corticothalamic (CT) feedback from layer 6 (L6) contributes to this enhancement (Andolina et al., 2012). Because L6 CT neurons are excitatory they can inhibit thalamic relay cells only indirectly via local geniculate interneurons or inhibitory neurons in the thalamic reticular nucleus (TRN). We hypothesized that if neurons in TRN were responsible for mediating feedback-induced surround suppression in dLGN, they should have large receptive fields (RF) and be suppressed if CT feedback is disrupted.

We tested this hypothesis by head-fixing C57BL/6 mice on a floating Styrofoam ball and recording extracellular single-unit activity using high-density silicon probes in the visual part of TRN (perigeniculate nucleus, PGN). For post-mortem confirmation of our recording site, we injected a retrograde AAV into dLGN leading in connected PGN neurons to the expression of green fluorescent protein. We presented full-field drifting gratings to identify visually responsive neurons and mapped their RFs with sparse noise stimuli. We measured surround suppression by showing drifting gratings of varying sizes.

We observed that activity in PGN was strongly modulated by behavioral state; thus, we restricted our analysis to trials, in which the animal was sitting. Numerous PGN neurons showed visually evoked responses at the temporal frequency of the drifting grating. Overall, PGN neurons had large RFs (mean = 19.6 deg^2), substantially exceeding the size of those in dLGN (mean = 3.3 deg^2, $p < 10^{-4}$). PGN RFs exhibited a rough topographic mapping, where units that resided more ventrally in the PGN tended to have lower RF centers. Examining responses to varying stimulus sizes revealed that PGN neurons exhibited a broad range of suppression strengths, including some weak ones.

Next, we tested how PGN responses are affected by CT feedback. In visual cortex (V1) of PV-Cre mice we used a viral approach to conditionally express Channelrhodopsin-2 in parvalbumin positive interneurons. Activating these neurons allowed us to suppress V1 activity and hence disrupt CT feedback to PGN. Suppression of CT feedback led to a substantial reduction of PGN responses (31.7 Hz vs. 10.9 Hz, $p = 0.02$).

We conclude that PGN, given its large RFs and its suppression during disruptions of CT feedback, might play an important role for feedback-mediated surround suppression in dLGN.

Disclosures: G. Born: None. **M.A. Spacek:** None. **C. Lao:** None. **L. Busse:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.05/HH11

Topic: D.07. Vision

Support: NSERC
CFI
Réseau de la recherche en santé de la vision FRQS

Title: Laminar origins of the cortical projections to the lateral posterior thalamic nucleus in the mouse

Authors: E.-M. FRIGON, R. TREMBLAY-LALIBERTÉ, S. STROMEI-CLÉROUX, *D. BOIRE
Anatomie, UQTR, Trois-Rivieres, QC, Canada

Abstract: Cortical feedback to thalamic nuclei is an important source of contextual modulation of sensory perception. The lateral posterior thalamus (LP) of rodents is a high-order thalamic nucleus that receive projections from primary visual cortex (V1) as well as from all extrastriate visual cortices. Recent studies suggest that high-order thalamic nuclei are implicated in predictive coding circuits that detect differences between bottom-up inputs and top-down predictions. Top-down corticofugal projections originate from subsets of layer 5 and 6 neurons and thought to act as drivers and modulators respectively. In addition, layer 6 neurons are believed to generate alpha oscillation of core thalamic neurons and layer 5 would convey prediction errors. Iontophoretic injections of cholera toxin B fragment (CTB) were performed in LP of adult C57BL6J mice. Retrogradely labelled neurons in cortical layers 5 and 6 were charted throughout the ipsilateral cerebral cortex (Neurolucida MBF Bioscience) and quantified. Labelled neurons were found in V1 and in all extrastriate areas in all cases. In V1, labeled neurons were more abundant in layer 6 than in layer 5. In the extrastriate visual areas, labeled neurons in layer 5 and 6 were found in a range of proportions and abundant in both layers 5 and 6. This contrasts with knowledge of visual cortex projections to the LP-Pulvinar in cats and primates in which cortical projections from V1 to the LP-Pul originate almost only from layer 5 and from both layers in extrastriate areas. This suggest that the functional impact of V1 on this high-order thalamic nucleus would be different in the mouse compared to cats and primates. This suggests that V1 of the mouse would exert mainly a modulatory role on LP neurons whereas V1 in the cat and primate would have a strong driving influence on LP. This could be a general pattern for cortical projections to high-order thalamic nuclei in rodents. Previous studies reported abundant retrogradely labeled layer 6 neurons in the primary somatosensory cortex following tracer injection in the high-order somatosensory thalamic nucleus Po. Areal differences in the ratio of layer 5 and layer 6 corticothalamic projection neurons further suggest that the cortical feedback input to the LP from extrastriate areas is functionally heterogeneous.

Disclosures: E. Frigon: None. **R. Tremblay-Laliberté:** None. **S. Stromei-Cléroux:** None. **D. Boire:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.06/HH12

Topic: D.07. Vision

Support: CIHR

Title: Modulatory signals from the visual cortex to the pulvinar increase along the hierarchical order of cortical areas

Authors: *R. ABBAS FARISHTA[1], D. BOIRE[2], C. CASANOVA[1]
[1]Sch. of Optometry, Univ. de Montréal, Montreal, QC, Canada; [2]Anatomie, UQTR, Trois-Rivieres, QC, Canada

Abstract: The Lateral Posterior (LP), a homologue of primate pulvinar, is a higher order (HO) thalamic nucleus with reciprocal connections with most visual areas of the cortex, providing alternative transthalamic pathways for the transmission of cortical information. Two types of axon terminals have been identified in cortico-thalamic (CT) pathways: the type I (modulators) and type II (drivers) characterized by thin axons with small terminals and by thick axons and large terminals respectively. Studies in our lab have shown that the projections from the cat primary visual cortex (V1) to the LP comprise mainly type II terminals whereas those from the PosteroMedial lateral Suprasylvian cortex (PMLS) comprise mainly type I. It is hypothesized that in HO thalamic nuclei, the proportion of type I/type II CT terminals would increase with the hierarchical level of visual areas. To test this hypothesis, we charted the distribution of CT terminals from area 21a, considered to be at a higher hierarchical level than the PMLS. The vast majority of terminals labelled in the LP were type I (77%) and formed small boutons located on short stalks of thin axons. Some terminals were larger than type I and located on thicker axons and were classified as type II (23%). None of the projections exhibited large terminals with complex rosette-like structures. Projections from V1 exhibited a higher number of type II terminals (75%) with single large boutons located on a long axonal side branch classified as singleton, and more complex rosette-like structures composed of three or more distinct swellings. In conclusion, the majority of the projections from the high order cortical area 21a in the LP exhibited a type I like morphology, suggesting that area 21a exerts mainly a modulatory influence on pulvinar. Our results further suggest that the number of modulatory cortical inputs to the pulvinar increases with the hierarchical order of cortical visual areas.

Disclosures: R. Abbas farishta: None. **D. Boire:** None. **C. Casanova:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.07/DP06/HH13

Topic: D.07. Vision

Support: Translational Neuroscience Initiative Grant, University of Pennsylvania

Title: Visually evoked gamma oscillations organize into standing, traveling and rotational waves that are detected in visual and association cortices in the anesthetized mouse brain

Authors: *A. AGGARWAL[1], C. BRENNAN[2], B. SHORTAL[2], A. MCKINSTRY-WU[3], D. CONTRERAS[2], M. B. KELZ[3], A. PROEKT[3]
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Neurosci., [3]Anesthesiol. and Critical Care, Univ. of Pennsylvania, Perelman Sch. of Med., Philadelphia, PA

Abstract: Visual stimuli induce a wave of neural excitation initially in a small region within the visual sensory cortex, that subsequently spreads across large areas of cortex and long outlasts stimulus presentation. Currently, the means by which this population evoked activity integrates with ongoing neural activity within the brain without distorting afferent information remains unknown. Here, we utilized isoflurane anesthesia to parametrically alter the spectral state of the brain of mice while recording visual evoked responses over an entire hemisphere with high-density electrocorticography (ECoG). We find that the shape of visual evoked potentials changes on a trial by trial basis, between anesthetic concentrations, and across individuals. However, there is a consistent visually evoked gamma band oscillation (30-50Hz) that is present in all mice, under all isoflurane concentrations, and in all trials. This gamma oscillation is coherent between trials in the early phase (<250 msec) of the visual evoked potential. There is also later (<300 msec) induced oscillation that peaks in power at 25Hz, which is not consistently in phase between trials. The early evoked 35 Hz gamma oscillations organize into standing, traveling and rotational wave patterns, which are present in primary and secondary visual cortices, the posterior partial association cortex, and the somatosensory cortices. These widespread evoked gamma oscillations that are prominent in multiple cortical regions may be important for global brain processing of multisensory stimuli, even in the unconscious brain.

Disclosures: A. Aggarwal: None. **C. Brennan:** None. **B. Shortal:** None. **A. McKinstry-Wu:** None. **D. Contreras:** None. **M.B. Kelz:** None. **A. Proekt:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.08/HH14

Topic: D.07. Vision

Support: Canada Research Chair in Cognitive Neuroscience
Natural Sciences and Engineering Research Council

Title: Neuronal mechanisms of motion detection underlying blindsight assessed with functional magnetic resonance imaging

Authors: *M. W. MACLEAN[1,4], V. HADID[2,4], L. LAZZOUNI[1,4], D. K. NGUYEN[3,5], F. LEPORE[1,4]
[1]Psychology, [2]Biomed. sciences, [3]Neurosciences, Univ. de Montréal, Montréal, QC, Canada; [4]Ctr. de Recherche en Neuropsychologie et Cognition, Montréal, QC, Canada; [5]Ctr. Hospitalier de l'Université de Montréal, Montréal, QC, Canada

Abstract: Patterns of unique functional neural activations correlated with a motion detection paradigm can illustrate the implication of alternative pathways allowing residual vision following visual impairment. Individuals with a clinical blind hemifield, caused by a unilateral post-chiasmatic lesion involving the striate cortex, report not seeing objects presented in their blind field, yet demonstrate the ability to detect, point towards and distinguish visual stimuli. This blindsight phenomenon represents a rare dissociation between consciousness and performance and is observed in homonymous hemianopia (HH) subjects with a contralateral visual loss. This study demonstrates cortical and subcortical structures involved in blindsight after a visual cortex lesion with blood oxygen level-dependant signal of functional magnetic resonance imaging (fMRI) using an event-related motion detection task. Whole brain and sliced thalamic fMRI scan sequences showed a reorganization in the structure and function of the visual pathways in HH individuals compared to neurotypical controls. Acquiring and associating neural correlates, specific structures and functional networks of the midbrain during blindsight performances represents a significant original contribution. Behaviourally, the presence of residual visual abilities was demonstrated through accurate performance rates, although with slower reaction times in the blind field. With respect to activations, when the normal hemifield was stimulated, significant contralateral activations were observed in primary and secondary visual areas as well as in motion specific areas, such as the supramarginal gyrus and middle temporal area, as well as sub-thalamic activations of the superior colliculi (SC) and pulvinar. These results attest the involvement of subcortical structures in spontaneous motion detection. When the blind hemifield was stimulated, contralateral activity in extrastriate areas was observed, with no activation of the primary visual cortex but robust activations of the SC.

However, unexpected ipsilateral cortical activations were observed within the same motion specific areas, as well as bilateral frontal activations. These results highlight the importance of secondary pathways bypassing the primary visual area (V1) in residual vision. The results elucidate the blindsight paradox and may potentially impact the development of restoration therapies targeting these alternative, in particular subcortical, pathways.

Disclosures: M.W. MacLean: None. **V. Hadid:** None. **L. Lazzouni:** None. **D.K. Nguyen:** None. **F. Lepore:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.09/HH15

Topic: D.07. Vision

Support: NIH Grant EY024946

Title: The synaptic impact of directionally selective LGN neurons on primary visual cortex

Authors: *Y. I. BERESHPOLOVA[1], C. R. STOELZEL[1], J. ALONSO[2], H. A. SWADLOW[1]
[1]Dept. of Psychology, Univ. of Connecticut, Storrs, CT; [2]Biol. and Visual Sci., SUNY Optometry, New York, NY

Abstract: Directional selective (DS) neurons are found in the retina and lateral geniculate nucleus (LGN) of rabbits and rodents. In the rabbit, LGN DS neurons are relatively rare (< 7%[1, 2, 3]), and most LGN neurons have concentric receptive fields. Notably, whereas most neurons in rabbit visual cortex (V1) are sharply tuned for orientation and direction[4, 5], the role of LGN DS neurons in V1 processing, and the laminar distribution of their axon termination sites, is unknown. Here, we investigated LGN DS neurons in awake rabbits, examined the laminar profile of presynaptic (axonal) and monosynaptic LFPs/currents generated in the retinotopically aligned region of V1 by these neurons, and compared these results for DS neurons with those of LGN concentric neurons. To do this, we first obtained extracellular recordings from LGN DS neurons using methods that yield stable, multi-day recordings. After characterizing their visual response properties, we identified the retinotopically aligned region of V1, and placed a 16-channel linear probe (Neuronexus) within this precisely aligned cortical region. We then studied the laminar profile of axonal and monosynaptic currents generated by spontaneous spikes of the LGN neurons. This method, single-axon spike triggered LFP/current source-density analysis, yields a view of the laminar profile of axonal and synaptic currents generated in the cortex by single thalamocortical neurons[2, 6-9].
We studied 14 LGN DS neurons in this manner, and our results are very similar to our previous results for LGN concentric neurons[2]. Thus, (1) the major synaptic impact of each LGN DS

neuron was in layer 4 and/or 6, with none showing a significant impact in superficial cortex. (2) Axonal conduction times of all DS neurons were short (range 0.65 - 1.8 ms), and (3) the monosynaptic thalamocortical responses exhibited prominent activity-dependent synaptic depression. We conclude that the presynaptic (axonal) and monosynaptic currents generated in V1 by the spikes of LGN DS neurons and concentric neurons are similar in their laminar profile, synaptic dynamics, and axonal conduction times, suggesting similar synaptic connectivity in layers 4 and 6, and similar roles in cortical functioning. References: 1. Swadlow, HA and Weyand, TG, *J. Neurophysiol*, 1985; 2. Stoelzel, CR et al., *J. Neurosci*, 2008; 3. Hei, X et al., *J. Neurophysiol*, 2014; 4. Swadlow, HA and Weyand, TG, J. Neurophysiol, 1987; 5. Zhuang, J et al., J. Neurosci, 2013; 6. Swadlow, HA et al., *J. Neurosci*, 2002; 7. Jin, JZ et al., *Nat. Neurosci*, 2008; 8. Jin, JZ et al., *Nat. Neurosci*, 2011; 9. Hagen, E et al., *J. Neurosci*, 2017

Disclosures: Y.I. Bereshpolova: None. **C.R. Stoelzel:** None. **J. Alonso:** None. **H.A. Swadlow:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.10/HH16

Topic: D.07. Vision

Support: NIH Grant EY022577
NSF GRFP

Title: Monosynaptic rabies tracing reveals input-output connections between visual cortex and the lateral posterior nucleus of the thalamus

Authors: *R. M. CASSIDY, E. M. CALLAWAY
The Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Higher-order visual thalamus is extensively connected to the visual cortex. Its outputs target both primary visual cortex (V1) and higher visual areas (HVAs), and its inputs come from those same regions. The pulvinar, the higher-order visual thalamus of primates, coordinates cortical activity according to behavioral demands (Saalmann et al., 2012; Zhou et al., 2016) and could hypothetically relay sensory information between visual areas (Sherman and Guillery, 2002). In the mouse, the lateral posterior nucleus (LP) is the analog to the pulvinar and shares its extensive cortical connectivity. To understand the specific circuits involved in these thalamocortical interactions, a precise map of the input/output connections of LP is needed. Cortical inputs to an LP projection population might originate from the target area, creating a reciprocal loop. Alternatively, they might originate from upstream or downstream areas, mirroring the direct corticocortical pathways. Corticothalamic projections can be “drivers”

originating in layer 5b or “modulators” from layer 6. This study characterizes the inputs to specific LP projection populations using intrinsic signal imaging (ISI) and monosynaptic rabies tracing. Our lab previously demonstrated that most LP neurons project to only one visual area. Therefore, we can access projection populations in LP using retrograde (AAVretro, Tervo et al., 2016) viral infection. Using male and female Ai14/Tlx3Cre mice, we generate a map of V1 and HVAs with ISI and target individual areas with an AAVretro virus expressing Flp recombinase. By injecting AAVs expressing Flp-dependent optimized rabies glycoprotein and a Flp-dependent TVA receptor fused to mCherry in LP, we are able to target specific projection populations for transynaptic tracing. After 21 days, we inject a pseudotyped EnvA, G-deleted rabies virus expressing GFP, which infects only those LP neurons projecting to a given HVA (starter cells). Mice are euthanized after another 7 days to allow for monosynaptic spread of the rabies virus from starter cells to input cells. Because the Ai14/Tlx3Cre mice express tdTomato in layer 5, we can assign a laminar location to the GFP+ input cells. Tangential cortical sections facilitate alignment with ISI maps. Our results show that many different visual areas provide input to a specific LP projection population, and this input originates from layer 5 and layer 6. We also find that the presence of tectal input to LP neurons is dependent on their cortical target. By fully characterizing the input/output connections of LP, these experiments add to our understanding of thalamocortical circuits and can inform future physiological studies.

Disclosures: R.M. Cassidy: None. **E.M. Callaway:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.11/HH17

Topic: D.07. Vision

Support: NIMH R01MH093413

Title: Hypersensitivity of the parvocellular visual pathway in trait-anxious individuals

Authors: *Y. YOU[1], W. LI[2]
[1]Psychology, [2]Dept. of Psychology, Florida State Univ., Tallahassee, FL

Abstract: Growing evidence from recent studies has revealed biases in basic visual processing among patients with psychiatric disorders such as autism, depression and schizophrenia (Butler & Javitt, 2005; Dakin & Frith, 2005; Fitzgerald, 2013). These patients exhibit unbalanced recruitment of parvocellular (P) and magnocellular (M) visual pathways, which are known to be segregated and tuned to distinct physical properties of the stimuli (Livingstone & Hubel, 1988). However, it is unclear whether such biases are tied to broad personality traits, such as trait anxiety. Across four independent studies, we assessed early visual evoked potentials (VEPs) to

stimuli designed to selectively activate the M and P pathways, in relation to different levels of trait anxiety. In keeping with previous findings, M- and P-selective stimuli evoked distinct early VEPs, implicating segregated neural pathways. We observed a positive-going P1 component (around 128 ms) for M-selective stimuli [i.e. low-spatial-frequency (LSF), low-contrast achromatic Gabor patches in Studies 1 & 2; LSF, low-contrast achromatic oval gratings in Study 3; and LSF, achromatic neutral scenes in Study 4] and two negative-going components, C1 (around 90 ms) and N1 component (around 120 ms), for P-selective stimuli [i.e. high-spatial-frequency (HSF), red-green isoluminant Gabor patches in Studies 1 & 2; HSF, low-contrast achromatic gratings in Study 3; and HSF, achromatic scenes in Study 4]. Importantly, individual levels of trait anxiety were positively correlated with the magnitudes of P-specific VEPs (C2 or C1) across all four studies (r's: .27~.40, p's: .016~.05), whereas the relations between trait anxiety and the magnitudes of M-specific VEPs were less clear [negative in Study 1 (r's: -0.42~-.39, p's: .004~.011), but not significant in the other studies (p's > .16)]. Furthermore, in Study 1, we assessed these VEPs among the same subjects at three time points (initial assessment, 30 minutes later, and 2 weeks later). Not only were the VEPs highly reliable over time, the correlation with trait anxiety was significant at all three assessments. Together, these results unveil a trait-like property of visual pathway sensitivity that varies with the level of trait anxiety. Specifically, trait anxiety is associated with hypersensitivity of the P visual pathway. A possible implication of this finding is that trait-anxious individuals are particularly tuned to visual input engaging the P pathway, which could underpin their tendency to perceive local (vs. global) features and explain their known bias to see the trees but not the forest.

Disclosures: Y. You: None. **W. Li:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.12/II1

Topic: D.07. Vision

Support: SFB1233 TP10
SFB870 B19
DFG BU 1808/5-1

Title: Effects of cortical feedback and behavioral state on naturalistic movie responses in mouse dLGN

Authors: *M. A. SPACEK[1], G. BORN[1,2], L. BUSSE[1,3]
[1]Div. of Neurobiology, Dept. Biol. II, LMU Munich, Planegg-Martinsried, Germany; [2]Grad. Sch. of Systemic Neurosciences, Munich, Germany; [3]Bernstein Ctr. for Computat. Neurosci., Munich, Germany

Abstract: Relay cells in the dorsal lateral geniculate nucleus (dLGN) of the thalamus receive feedback from primary visual cortex (V1) layer 6 corticothalamic (CT) neurons, via both direct excitation and disynaptic inhibition. How does CT feedback modulate responses in dLGN? Past studies using simple grating visual stimuli have shown diverse effects [1-3], but CT feedback might be particularly relevant during processing of complex visual stimuli, and its effects might depend on behavioral state [4].

We examined how CT feedback and behavioral state shape responses to naturalistic movie clips. Channelrhodopsin-2 (ChR2) was conditionally expressed in V1 of PV-Cre mice by local viral injection (AAV9). Activity in V1 was suppressed by optogenetic activation of parvalbumin (PV) positive interneurons, thereby suppressing CT feedback. Mice were head-fixed, but free to sit or run on a floating ball, while single unit responses in dLGN were recorded with high-density silicon probes. Grayscale naturalistic movies of mostly foliage (5 s long, 60 fps) with motion simulating saccades/head movements (up to 275 deg/s), were presented full screen on an LCD (108 x 68 deg) for 100s of trials per experiment.

dLGN responses to movies were generally sparse and reliable, with spikes often concentrated into short periods of time within each trial, separated by periods of relative silence. Responses were characterized by their mean firing rates, sparseness [5], reliability [6], and burst ratio [7]. Regardless of behavior, feedback increased mean firing rates ($p < 10^{-6}$), and decreased sparseness ($p < 10^{-8}$) and burst ratio ($p < 10^{-5}$), compared to when feedback was suppressed. Similarly, regardless of feedback, running increased mean firing rates ($p < 10^{-9}$), and decreased sparseness ($p < 10^{-9}$), reliability ($p < 10^{-6}$) and burst ratio ($p = 0.008$), relative to periods of sitting. The effects of feedback and behavioral state on dLGN were generally independent for all 4 response measures.

With feedback and during running, responses were more tonic, while without feedback and during sitting, responses were more burst-like. The presence or absence of either feedback or running may switch dLGN between burst and tonic mode firing. Because feedback and running have independent effects, this could be via separate mechanisms. Given the tradeoffs between tonic and burst mode firing [8], feedback and running may make dLGN encode stimulus information more linearly, while their absence might make dLGN more sensitive to salient events.

1. Sillito et al., 2006; 2. Olsen et al., 2012; 3. Denman & Contreras, 2015; 4. Briggs & Usrey, 2008; 5. Vinje & Gallant, 2000; 6. Goard & Dan, 2009; 7. Wang et al., 2006; 8. Sherman, 2001

Disclosures: M.A. Spacek: None. **G. Born:** None. **L. Busse:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.13/II2

Topic: D.07. Vision

Support: NIH DP2 EY024504
Canadian Institutes of Health Research Postdoctoral Fellowship
Knights Templar Eye Foundation

Title: Role of early visual experience in shaping binocularity in the thalamocortical pathway

Authors: *C. HUH[1], K. ABDELAAL[1], K. J. SALINAS[1], D. GU[2], J. ZEITOUN[1], D. X. FIGUEROA VELEZ[1], J. P. PEACH[4], C. FOWLKES[3], S. P. GANDHI[1]
[1]Neurobio. and Behavior, [2]Statistics, [3]Computer Sci., Univ. of California Irvine, Irvine, CA; [4]Whiting Sch. of Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Recent research indicates that binocular integration occurs at multiple stages of the central visual pathway, including in the dorsolateral geniculate nucleus (dLGN) of the thalamus. How binocular information is relayed and transformed at each stage of visual processing remains incompletely understood. Moreover, the role of early visual experience in the development of dLGN binocularity is unclear. To address these issues, we performed in vivo two-photon calcium imaging of dLGN axons innervating superficial layers of V1. A calcium sensor, GCaMP6s, was specifically targeted to thalamic neurons using VGLUT2-Cre mice and Cre-dependent viral GCaMP6s expression. We measured the responses of dLGN boutons in superficial layers of binocular V1 to drifting gratings in awake, head-fixed adult mice. Bouton responses were compared between normal mice and mice that were monocularly deprived (MD) during the critical period for visual development (postnatal days 19-33); in MD mice, dLGN bouton responses were recorded from V1 contralateral to the deprived eye. We found that in normal mice, 10% of visually responsive dLGN boutons exhibited significant responses to both eyes (i.e., binocular). Interestingly, binocular bouton responses were much stronger than monocular bouton responses. In comparison, ~30% of V1 L2/3 neurons were binocular and their responses were only slightly stronger than those of monocular neurons. Overall, dLGN boutons were tuned to higher spatial frequencies (SF) than V1 neurons; binocular and monocular boutons displayed a median peak SF of 0.12 cpd compared with 0.06 cpd in V1 neurons. Binocular boutons were relatively well-matched in terms of SF preference; 45% of binocular boutons showed matched peak SF between contralateral- and ipsilateral-eye responses. We found that MD had multiple long-lasting deleterious effects on dLGN boutons. Overall, 30% fewer visually responsive dLGN boutons were recorded per field of view in MD mice compared with control mice. Binocular boutons were particularly affected; only 3% of all visually responsive boutons were binocular in MD mice, a 67% reduction compared with control mice. In the remaining binocular boutons, MD led to a significant mismatch in preferred SF between the eyes (only 13% matched in peak SF) without a significant reduction in response amplitude. These findings indicate that binocular dLGN axons supply the visual cortex with high-fidelity visual inputs that are particularly vulnerable to monocular deprivation during the critical period. Binocular input from the dLGN may play an important role in the critical period for the development of binocular vision.

Disclosures: C. Huh: None. **K. Abdelaal:** None. **K.J. Salinas:** None. **D. Gu:** None. **J. Zeitoun:** None. **D.X. Figueroa Velez:** None. **J.P. Peach:** None. **C. Fowlkes:** None. **S.P. Gandhi:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.14/II3

Topic: D.07. Vision

Support: NSERC Grant RGPIN-05394
NSERC Grant RGPAS-477166

Title: Modulation of binocular rivalry with monocular visual tetanization and non-invasive stimulation of the visual cortex

Authors: *D. ABULEIL, D. L. MCCULLOCH, B. THOMPSON
Univ. of Waterloo, Waterloo, ON, Canada

Abstract: Purpose: Binocular rivalry (BR) alternation rates have been associated with primary visual cortex GABA concentration, whereby faster alternation rates are correlated with lower GABA levels. In addition, the relative input strength from each eye affects BR dynamics. We assessed the effect of three neuro-modulation techniques on BR. The first two techniques, anodal transcranial direct current stimulation (a-tDCS) and intermittent thetaburst transcranial magnetic stimulation (iTBS) reduce and increase GABA concentration in the motor cortex respectively. If similar effects occur over the visual cortex, the two techniques should have opposing effects on BR alternation rates. Rapid visual tetanization induces stimulus-specific LTP within the visual cortex. Therefore, monocular tetanization (MT) should increase perceptual dominance of the tetanized eye during BR. **Methods and Materials:** Alternation rates were recorded using dichoptic red/green orthogonal gratings (0.5cpd) before and after MT (N=20 active, 20 controls), tDCS (N=15 active, 7 controls) or iTBS (N=9 active, 9 controls). The gratings were presented for a minimum of 3 min and participants indicated red, green or piecemeal percepts using a button press. MT involved passive monocular viewing of the red or green grating flickering at 9Hz for 2 min followed by 2 min of eye closure. The control condition was identical except that both the red and green gratings were viewed binocularly. a-tDCS involved 15 min of 2mA (active) or sham (controls) stimulation (anode Oz, cathode Cz). iTBS involved 600 pulses delivered over V1 in 50Hz bursts for 40 sec at 100% of active motor threshold. The control condition used the same protocol with a sham coil. **Results:** a-tDCS and iTBS had no effect on BR dynamics. MT did not affect alternation rates but did significantly increase the duration of piecemeal percepts ($t_{19} = 2.9957$, $p < 0.01$). **Discussion and Conclusion:** a-tDCS and iTBS did not modulate BR alternation rates as predicted. This may indicate that motor cortex GABA concentration changes induced by these techniques do not occur for the visual cortex. Alternatively, GABA modulations induced by non-invasive brain stimulation may not exert an

effect on perception. Rather than increasing the dominance of the tetanized eye, MT reduced BR leading to increased piecemeal percept durations.

Disclosures: D. Abuleil: None. **D.L. McCulloch:** None. **B. Thompson:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.15/II4

Topic: D.07. Vision

Support: NIH Grant 1R01EY027402-02
NIH grant 5T32 EY007135-23

Title: Monocular V1 neurons are sensitive to both eyes

Authors: *K. DOUGHERTY[1], M. A. COX[2], J. A. WESTERBERG[2], A. V. MAIER[1]
[1]Dept. of Psychology, [2]Vanderbilt Univ., Nashville, TN

Abstract: Our brains combine the separate outputs of the two eyes, which leads to a singular view of the visual field. Where this combination occurs in the primate primary visual pathway remains an open question. Receiving the main projections from the retina, neurons in the lateral geniculate nucleus of the thalamus (LGN) are excited by stimulation of one eye and not the other, and for this reason are called monocular neurons. Next, in the primary visual cortex (V1), many neurons are excited by stimulation of either eye, and for this reason are called binocular. Because most V1 neurons are binocular, some form of binocular combination is thought to have occurred once these neurons fire. However, where within the V1 laminar microcircuit this binocular combination first occurs is unclear. We asked where binocular combination first occurs in the V1 laminar microcircuit by testing the degree to which macaque V1 neurons in all layers are sensitive to stimulation of one or both eyes. We found that more than 94% of V1 neurons were binocular, driven by stimulation of either eye. Congruent with previous work, monocular neurons were primarily located in the main geniculate input layer of V1. Surprisingly, we found that while these monocular neurons were excited by one eye only, they also showed systematic firing rate differences between stimulation of their driving eye alone compared to stimulation of both eyes. This finding suggests that V1 monocular neurons encode what is shown to both eyes. We conclude that, while V1 geniculate inputs are primarily separated by eye, the outputs of their V1 target neurons are sensitive to what both eyes view, suggesting binocular combination in the primate visual system occurs either before or at the initial cortical processing stage.

Disclosures: K. Dougherty: None. **M.A. Cox:** None. **J.A. Westerberg:** None. **A.V. Maier:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.16/II5

Topic: D.07. Vision

Support: Human Frontiers Science Program
NIH Grant EY025102
NIH Grant EY020592

Title: Optokinetic eye movements in mouse to stereoscopic motion

Authors: *V. CHOI[1], N. J. PRIEBE[2]
[1]Dept. of Neuroscience, Ctr. for Perceptual Systems, Ctr. for Learning a, Univ. of Texas at Austin, Austin, TX; [2]Univ. Texas, Austin, Austin, TX

Abstract: Vertebrates make eye movement to stabilize moving objects. One such eye movement is the optokinetic reflex (OKR) which is an involuntary conjugate eye movement. The OKR also evokes vergence eye movements in primates when an object moves in depth (Busettini et al.,1996; Kodaka et al.,2007; Inoue et al.,1998; Yang et al.,2003; Sheliga et al.,2016). These vergence eye movements reflects the binocular integration of visual signals. To demonstrate that mice, a mammal with laterally placed eyes, also perform binocular integration, and gain access to the the underlying neuronal mechanisms for OKR, we examined vergence eye movements in awake mice viewing stereoscopic stimuli. Random dots were presented that contained both interocular velocity difference (IOVD) and change in disparity (CD) signals using polarizing lenses. The dots were presented such that they moved smoothly in a sinusoidal motion towards and away from the animals. We found vergence eye movement associated with random dot stereogram stimuli similar to what has been reported in primates. The two eyes converged when the dots moved in the toward direction and diverged when the dots moved in the away direction. We also found that IOVD signal is crucial for the optokinetic reflex (OKR) as eliminating the IOVD signal diminished the eye movement associated with the stimuli. In contrast, eliminating the disparity signals had little impact on the vergence eye movements. Finally we assayed the role of cortical processing in this behavior by silencing visual cortex while presenting the toward and away motion. We found that cortical silencing also had little impact on vergence eye movements. These results indicate that IOVD signals provide the dominant input to vergence OKR in mice and that the visual cortex plays little role in these eye movements. The binocular computation required for these vergence eye movements likely occurs in subcortical structures.

Disclosures: V. Choi: None. **N.J. Priebe:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.17/II6

Topic: D.07. Vision

Title: Ocular dominance and homeostatic opponent cortical processing

Authors: *D. Y. TS'O, R. MILLER
Dept of Neurosurg., SUNY - Upstate Med. Univ., Syracuse, NY

Abstract: The classical view of binocular interactions in primate V1 is one of competition between the two eyes, at least during the development of the ocular dominance (OD) columns, if not also in adult life. Yet there is also evidence for ongoing interocular cooperativity and homeostatically-regulated balance. A re-examination of OD data from optical imaging studies suggests an interocular process that seeks to maintain a set level of left/right eye opponency (an L-R signal) atop other ongoing cortical activity.
Optical imaging of OD columns (ODCs) is performed by acquiring sets of V1 images during left eye (L), right eye (R), both eye (binocular) and no eye (blank) stimulation. Invariably and surprisingly, the OD (L-R) image yields a far "cleaner" spatial (functional organization) map of the ODCs than is observed in the "single condition" maps (e.g. L-blank). Extracting a line profile across the ODCs in an L-R map confirms a smooth, nearly sinusoidal OD signal. This OD signal exhibits near-zero DC offset, indicating normally well-matched inputs from the two eyes. In contrast to the OD (L-R) signal, the line profiles derived from the L or R single-condition maps appear more disjoint and irregular with the ODC signal often buried. The calculation of L-R is equivalent to removing the "cocktail blank", i.e. removing common mode cortical activity signal. The common mode activity includes a binocular response component that might explain the robust L-R maps by “washing out” the ODC signal in single-condition maps. A comparison of the response to binocular vs monocular stimulation revealed a 1.5X to 2X increase in cortical activity under binocular stimulation that may correspond to the classical advantage afforded by binocular summation. This analysis however, allows for the isolation of the binocular-only cortical activity and shows that it cannot explain the surprisingly robust L-R signal.
Similarly, short-term monocular deprivation (STMD) experiments in which a 1-2 hour monocular deprivation yielded a disruption of interocular balance and monocular gains lasting an hour. Yet immediately following STMD, the OD (L-R) signal "bounced back" to near normal amplitude and form even though each eye's activity had not yet returned to baseline. The implication is that homeostatic V1 circuits regulating interocular gain strive for a robust OD (L-R) spatial signal despite local and monocular perturbations, perhaps a by-product of maintaining proper interocular balance.

Disclosures: D.Y. Ts'o: None. **R. Miller:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.18/II7

Topic: D.07. Vision

Support: RRSV 3738-2016
ERA-NET NEURON JTC 2015

Title: Interocular normalization in monkey primary visual cortex

Authors: *A. REYNAUD[1], S. ROUX[2], S. CHEMLA[2], F. CHAVANE[2], R. HESS[1]
[1]McGill Univ., Montreal, QC, Canada; [2]CNRS, Marseille, France

Abstract: The slight difference in the signals coming from the two eyes is used by our brain to compute a tridimensional representation of the visual world. The monocular inputs reach the cortex in layer 4 in segregated ocular dominance domains. Then they are first combined by binocular neurons in layer 2/3. Studying how the information coming from the two eyes is integrated in ocular dominance map's referential at the mesoscopic scale is however still unknown. For this purpose, we used voltage sensitive dye imaging (VSDI) in anesthetized and awake behaving monkeys to analyze how these signals are integrated and summed at the population level in V1.
In order to identify the signals originating from the two eyes, we used a steady-state frequency-tagging paradigm. Visual stimuli of different contrasts were presented at 6Hz and 10Hz to the left and right eye respectively, separately or simultaneously with a passive 3D monitor. The frequency analysis of the evoked response was used to identify the contribution of each eye. We observed that the population activity in V1, elicited by the stimulation of one eye, is suppressed by a dichoptic stimulation compared to monocular stimulation. This signal integration was accurately accounted for by an interocular normalization model of population activity.
These approach and model confirm an implication of V1 population in the combination of the two eyes signals. Whether this normalization originates locally, or from feedback, feedforward or long range connectivity remains to be investigated.

Disclosures: A. Reynaud: None. **S. Roux:** None. **S. Chemla:** None. **F. Chavane:** None. **R. Hess:** None.

Poster

669. Visual Pathways: To and From the Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 669.19/II8

Topic: I.02. Systems Biology and Bioinformatics

Support: NIMH/NIH R01MH100635

Title: Novel evidence of high resolution and high field diffusion mri reveal a primate lgn-lgn connection

Authors: J. R. KORENBERG[1], L. DAI[2], D. PRITCHETT[3], A. VAN HOEK[4]
[1]Brain Institute, Pediatrics, [2]Dept. of Pediatrics, Univ. of Utah, Salt Lake Cty, UT; [3]Korenberg Research/Neurology, [4]Neurol., Univ. of Utah, Salt Lake City, UT

Abstract: Establishing a primate brain connectivity and linking it function and human diseases remain an elusive goal. Diffusion MRI, which quantifies the magnitude and anisotropy of water diffusion in brain tissues, offers unparalleled opportunity to link the macroconnectome to histological-based microconnectome at synaptic resolution, providing opportunity to confirm the known connection and propose novel connection. In this report, we show evidence using high resolution diffusion spectrum imaging (DSI) in primate brain to support the existence of a novel brain connection between the left and right lateral geniculate nucleus (LGN). We obtained high resolution diffusion MRI data on *ex vivo* brain from Macaca fascicularis: MRI 7T, resolution 0.5 mm isotropic, 515 diffusion volumes up to b-value (aka diffusion sensitivity) of 40,000 s/mm^2 with scan time ~100 hrs. Tractography results show direct connection between the left and right LGN. This finding is supported by previous functional and neuroanatomic data. First, Gitlin and Lowental (1969), reviewing 150y of literature including and post Gudden, there is no evidence from either Gudden or others, for the existence of a commissure connecting the two medial geniculate (MGN) in humans or even rabbits. Rather, the "medial root of the optic tracts" likely is what has been seen connecting the optic chiasma-related to optic tract bulges that go to the ventral medial aspect of the LGN. Second, although a number of very well done papers referred to above, identify other tracts in the region, no reports find or confirm the predicted Commissure of Gudden. It is interesting that Dougherty's review (2018) set out the possible modulatory circuitry responsible for binocular modulation, in the LGN, something they refer to as "an apparent paradox", and note that this may be explained not only by their proposals but also "through mechanisms yet to be uncovered". We propose that simplest explanation for their data may be found in the multiple paths of evidence for the LGN-LGN connection supported by our new finding. In conclusion, by combining the previous data in literature and our new tractography results, we hypothesize that there is direct LGN-LGN connection, and this finding will provide a flush of new interest and funding for the field to identify the mechanisms, the

molecules responsible, the embryo/fetogenesis and pruning, and the consequences for disease malfunction and correction.

Disclosures: J.R. Korenberg: None. **L. Dai:** None. **D. Pritchett:** None. **A. Van Hoek:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.01/II9

Topic: E.03. Basal Ganglia

Support: ANR-11-LABX-0042
CRSII3-141965

Title: Methylphenidate and fluoxetine improve approach-avoidance task in non-human primate: A behavioral study associated to PET imaging

Authors: M. MILLOT[1], E. MARTINEZ[1], G. DRUI[2], Y. SAGA[3], E. METEREAU[1], P. N. TOBLER[4], *V. SGAMBATO[5], L. TREMBLAY[1]
[1]Neurosci. Cognitive Ctr. - CNRS UMR 5229, BRON, France; [2]CNRS UMR5229 - Ctr. of Cognitive Neurosci., BRON, France; [3]Ctr. de Neurosci. Cognitive, Bron Cedex, France; [4]Univ. of Zurich, Zurich, Switzerland; [5]UMR 5229 - Inst. des Sci. Cognitives Marc Jeannerod, CNRS & Univ. Lyon 1, Bron Cedex, France

Abstract: The dopamine (DA) and serotonin (5-HT) systems are the two major neurotransmitters targeted in several neuropsychiatric disorders affecting motivation, value-based decisions and the context-adapted behaviors (approach or avoidance). The broad spectrum of processes on which DA can be involved is coming from its actions on Basal Ganglia (BG) that are partitioned into different functional territories. The 5-HT system that projects on a larger number of cerebral structures, especially limbic territories, also projects on BG. Their therapeutic actions in motivation and anxiety-relative behaviors could thus passed by the same BG territories also modulated by DA. To test this hypothesis, we compared the effects of DA and 5-HT treatment on 4 monkeys trained to perform an approach/avoidance task in which they had to adapt a behavior (approach or avoidance) in an appetitive (reward) or aversive (air puff) contexts. During this task, the CS provides essential information to select the context-adapted behaviors. To modulate the DA and 5-HT systems, we used drugs that act as a reuptake inhibitor; fluoxetine (FLX) at 4 mg/kg for the 5-HT system and methylphenidate (MPH) at 0.1 and 0.6 mg/kg for DA modulation. These drugs were tested on task performance and positron emission tomography (PET) imaging, using [^{11}C]DASB for the 5-HT transporter (SERT) and [^{11}C]PE2I for the DA transporter (DAT). First, we observed that both drugs induced, for all monkeys, an increase of completion rate (number of daily completed trials) reflecting an increase of

motivation. This benefit effect of both drugs was associated to a strong reduction of two behavioral markers of anxiety expressed in aversive context, non-initiated choices and escape behaviors in risky condition. This behavioral results shown that both drugs, DA and 5-HT, have benefit effects on motivation and anxiety. Secondly, the PET imaging investigation shown that the therapeutic dose of FLX led to a decrease of DASB binding in limbic cortical regions and also in ventral striatum, the putamen and the anterior caudate nucleus where the MPH led to a decrease of PE2I binding. These results allow us to highlight the importance of serotonin and dopamine modulation inside the BG, especially the striatum to modulate motivational disorders and anxiety-relative disorders.

Disclosures: M. Millot: None. **E. Martinez:** None. **G. Drui:** None. **Y. Saga:** None. **E. Metereau:** None. **P.N. Tobler:** None. **V. Sgambato:** None. **L. Tremblay:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.02/II10

Topic: E.03. Basal Ganglia

Support: 1R01-NS-077730-01A1

Title: A rodent two-hit model of task-specific dystonia

Authors: *K. KERNODLE[1], W. T. DAUER[2], D. K. LEVENTHAL[3,2]
[1]Neurosci. Grad. Program, [2]Neurol., Univ. of Michigan, Ann Arbor, MI; [3]Neurol., VA Ann Arbor Hlth. Syst., Ann Arbor, MI

Abstract: Task-specific dystonia typically develops after extensive training on specific tasks. Such tasks are typically highly dexterous, such as writing or playing a musical instrument. A prominent hypothesis posits that excessive repetitive training stresses normal plasticity processes, causing abnormal sensorimotor associations. We have developed a “two-hit” model for the pathogenesis of task-specific dystonia, by challenging mice carrying a human dystonia mutation with an environmental trigger. The mice lack torsinA in forebrain neurons and have no abnormal movements at baseline. These mice develop task-specific abnormal movements after repeated training on the dexterous single pellet skilled reaching task. In contrast, they do not develop any abnormal movements following repeated training on the non-dexterous rotarod task. These results support a two-hit model of dystonia pathogenesis and establish a model that will enable unique studies of dystonia pathogenesis and pathophysiology.

Disclosures: K. Kernodle: None. **W.T. Dauer:** None. **D.K. Leventhal:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.03/II11

Topic: E.03. Basal Ganglia

Support: Russian Science Foundation - RScF 18-15-00009
DMRF

Title: Single unit activity patterns of globus pallidus in patients with cervical and generalized dystonia

Authors: *A. SEDOV[1], S. USOVA[1], A. TOMSKIY[2], V. POPOV[2], A. GAMALEYA[2], R. MEDVEDNIK[1], A. G. SHAIKH[3]
[1]Lab. of human cell neurophysiology, Semenov Inst. of Chem. Physics, Russian Aca, Moskva, Russian Federation; [2]Burdenko Res. Ctr. of Neurosurg., Moscow, Russian Federation; [3]Neurol., Case Western Reserve, Cleveland, OH

Abstract: Dystonia is a movement disorder characterized by sustained muscle contractions, twisting, repetitive movements, and abnormal postures of the affected body part. Increasing evidence has suggested involvement of neural circuit connecting the sensorimotor cortex (SMC), the basal ganglia, and the ventrolateral thalamus. The globus pallidus internus (GPi) of the basal ganglia plays a critical role in this circuit. Decreases and increases in discharge of the GABAergic neurons of GPi could facilitate and suppress, respectively, the activity of recipient thalamocortical circuits and, eventually, the muscle activity. We propose that among with firing rate changes there are significant changes in spiketrain patterns in dystonia patients. We used microelectrode recording (MER) of GPi and GPe cells to analyze the differences of pallidal patterns in patients with cervical (CD) and generalized (GD) dystonia. The data was obtained during microelectrode-guided stereotaxic DBS surgeries. We used asymmetry index (AI) to separate tonic (AI>0,7) and burst (AI<0,7) cells. We measured 25 objective spike train parameters for each cell types. We estimated oscillations scores (OS) for each frequency band: theta, alpha, beta and gamma.We found robust differences in tonic and burst cells distributions in both GPi and GPe segments between CD and GD patients. CD patients had more tonic cells, while GD had more burst cells. There were no significant changes in indices of tonic or burst GPi cell discharge, with an exception of differential entropy, which was higher in GD patients and theta oscillations, which was higher in CD patients. At the same time, we didn't find any changes in GPe cells. Our finding showed the differences in burst and tonic cells distribution with no changes of unit activity patterns. We showed that GD patients are more bursty. Our results can be explained by the imbalance of direct pathway.

Disclosures: A. Sedov: None. **S. Usova:** None. **A. Tomskiy:** None. **V. Popov:** None. **A. Gamaleya:** None. **R. Medvednik:** None. **A.G. Shaikh:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.04/II12

Topic: E.03. Basal Ganglia

Support: NIH/NINDS grant R01-NS100908
NIH Office of Research Infrastructure Programs OD P51-OD011132 to the Yerkes National Primate Research Center

Title: Temporal variability in the firing of external globus pallidus neurons in monkeys

Authors: *A. GALVAN, X. HU, A. DEVERGNAS, T. WICHMANN
Yerkes Natl. Primate Res. Ctr. and Dept. of Neurology, Sch. of M, Emory Univ., Atlanta, GA

Abstract: Based on extracellular recordings obtained *in vivo* in monkeys, most neurons in the external segment of the globus pallidus (GPe) show high frequency firing interspersed by pauses while a smaller proportion of neurons show low frequency firing with bursts. Traditionally, these two patterns of firing have been considered to arise from distinct subpopulations of GPe neurons, but it is possible that the heterogeneity of firing patterns originate, instead, from temporal variations in the firing behavior of individual neurons. In rodents, GPe neurons show significant variation in firing rates across several minutes of recording (Diester et al, 2013). To examine the temporal stability of GPe neuronal firing in monkeys, we obtained long duration (10-60 min) recordings of well-isolated GPe neurons. Two monkeys (one male, one female, young adults) were prepared with chronic recording chambers aimed at the GPe. Extracellular recordings were conducted using tungsten electrodes and standard recording procedures, while the monkeys were sitting on a primate chair. The data was collected to a computer disk and spikes sorted. Timings of spikes were converted to inter-spike intervals (ISIs) for further analysis. The data were binned in one-minute bins, and for each bin we obtained several firing parameters (firing rate, ISI-coefficient of variability (ISI-CV), bursting parameters). We then calculated the maximal change observed (highest value minus lowest value) for each parameter during the recorded time. In most of the recorded 58 GPe neurons, substantial changes in firing parameters were seen across the recorded time. The firing rate changed (from minimal to maximal values obtained throughout recording), in average, 445% (SD 430%); while ISI-CV changed 291% (SD 289%), and the time the neurons spent in bursts changed in average 307% (SD 312%). We are currently in the process of studying the relationship of these long-term shifts in firing patterns to subtle changes in the state of wakefulness of the animals (based on analyses of electrocorticogram signals). Our results suggest that the firing of individual GPe neurons shows very high temporal variability. This

could explain, at least in part, the heterogeneous firing patterns that have been ascribed to GPe neurons in *in vivo* monkey recordings.

Disclosures: A. Galvan: None. **X. Hu:** None. **A. Devergnas:** None. **T. Wichmann:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.05/II13

Topic: E.03. Basal Ganglia

Support: CIHR grant MOP 53339)

Title: The contribution of the globus pallidus and the entopeduncular nucleus to the preparation and execution of voluntary gait modifications in the cat

Authors: *Y. MULLIE, I. ARTO, J. A. LEONARD, T. DREW
Dept. de Neurosciences, Univ. de Montreal, Montreal, QC, Canada

Abstract: The locomotor deficits observed in Parkinson's disease suggest that the basal ganglia (BG) exert a strong effect on the control of locomotion. However, despite this, we have little information on the properties of neurones in different parts of the BG circuit during this essential behaviour. In this study we examined the discharge patterns of neurons in the globus pallidus (GP) and the entopenduncular nucleus (EN) (equivalent to the external and the internal segment of the primates' pallidum, i.e. GPe and GPi respectively) of 4 cats during unobstructed locomotion and during visually guided locomotion as cats stepped over obstacles attached to a moving belt. Most neurons recorded in both nuclei (N=250) showed relatively high discharge at rest (10-72 Hz) and showed either no, or relatively weak, modulation of their discharge pattern during unobstructed locomotion. When the cats stepped over an obstacle, 125/250 showed modification of their activity related to the step over the obstacle by the forelimb contralateral to the recording site. In most cells, in both nuclei, the change in activity during the step over the obstacle, as compared to that during unrestricted locomotion was relatively weak, although some cells in both nuclei did show robust changes in activity. In both nuclei, most cells discharged either just before or during the gait modification of the contralateral forelimb (coFL) (step-related cells: EN 63/75, 85% and GP, 33/50, 66%). The other modified cells (EN, 12/75, 16% and GP, 17/50, 34%) showed weak sustained activity prior to the gait modification and were classified as step-advanced cells. A substantial proportion of the step-related cells in the EN showed either a single period of increased (12/63, 19%) or decreased (13/63, 21%) activity during the step over the obstacle by the coFL. Other cells in the EN showed either increased activity related to the coFL regardless of whether the contralateral or ipsilateral forelimb was the first to step over the obstacle (9/63, 14%), or reciprocal changes in activity (8/63, 13%). Cells

showing increased activity related to the coFL regardless of lead limb were more prevalent in the GP 11/33, 33%). The results suggest that the EN exerts a more focused effect on limb activity than the GP, compatible with a view that the EN(Gpi) is more involved in specifying the required movement while the GP (GPe) may be more involved in producing anticipatory changes prior to the movement and in modulating activity in both forelimbs. Nonetheless, there was also substantial overlap in the discharge patterns observed in each nucleus.

Disclosures: Y. Mullie: None. **I. Arto:** None. **J.A. Leonard:** None. **T. Drew:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.06/II14

Topic: E.03. Basal Ganglia

Title: Neuronal correlates of beat-based timing in the primate striatum

Authors: *M. KAMEDA[1], S. OHMAE[2], M. TANAKA[1]
[1]Med., Hokkaido Univ., Sapporo-Shi, Japan; [2]Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Both the basal ganglia and cerebellum are implicated in "beat-based timing" for isochronous repetitive events. To clarify how neurons in these areas represent event timing, we trained monkeys to perform the missing oddball task, in which temporal prediction of periodic visual stimuli was needed. We previously found that neurons in the cerebellar dentate nucleus (DN) showed temporally specific firing modulation during the task (Ohmae et al., 2013). In this study, we examined neuronal activity in the caudate nucleus and compared them with those recorded previously from the DN. So far, we have recorded from 84 neurons exhibiting a gradual increase of response to each stimulus as the repetition progressed, like neurons in the cerebellum. However, unlike neurons in the DN, many striatal neurons (87%) also exhibited a transient activity around the time of saccades. Furthermore, approximately 24% (12/50) of striatal neurons exhibited greater firing modulation for shorter inter-stimulus intervals, while the majority of neurons in the striatum and all neurons in the DN showed a preference for the longest interval. To clarify the functional difference, we assessed how precisely the time courses of neuronal activity predicted the next stimulus timing. Assuming that stimulus timing was predicted when the population activity surpassed a certain threshold, we searched for the optimal threshold that minimized the prediction error of the next stimulus timing (Δt) in trials with three inter-stimulus intervals (300, 400, 600 ms). We found that stimulus timing was better predicted by neuronal signals in the DN than the striatum ($\Delta t = 65 \pm 22$ ms vs. 28 ± 17 ms, bootstrap mean ± 95% CI). We also attempted to dissociate sensory from motor-related signals by locating repetitive visual stimuli and saccade target independently in either or both visual hemifields. Although most

neurons in both structures showed a significant interaction, we found that many neurons in the striatum exhibited greater firing modulation for saccade direction, while those in the cerebellar DN exhibited greater modulation for stimulus location. These results suggest that neurons in the striatum might be involved in the prediction of motor timing while those in the cerebellum in the prediction of sensory timing.

Disclosures: M. Kameda: None. **S. Ohmae:** None. **M. Tanaka:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.07/II15

Topic: E.03. Basal Ganglia

Support: NINDS Grant U01NS098961

Title: Spectral-spatial separation of motor conflict and stopping in the basal ganglia-cortical circuits

Authors: *J. CHOI[1], M. MALEKMOHAMMADI[1], S. NIKETEGHAD[2], A. R. ARON[3], U. RUTISHAUSER[4], N. POURATIAN[1]
[1]Neurosurg., [2]Bioengineering, UCLA, Los Angeles, CA; [3]Psychology, UCSD, San Diego, CA; [4]Neurosurg., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Introduction: Action regulation and suppression are key parts of everyday behavior. This includes suppressing competing actions when initiating a specific action, suppressing all responses when presented with conflicting information, and suppressing a response when the environment rapidly changes indicating a pre-planned response must be stopped. Our overall hypothesis is that action suppression during conflict and stopping involve dissociable fronto-basal ganglia (BG) circuits. **Methods:** We took advantage of deep brain stimulation surgery for Parkinson disease, to obtain cortical and BG recordings across two action suppression tasks (Eriksen flanker task and stop signal task). We recorded local field potentials from multi-site frontal cortical regions including motor cortex, pre-supplement motor area (pre-SMA), and right inferior frontal gyrus (rIFG) and BG including subthalamic nucleus (STN) and globus pallidus (GP). **Results**: Specifically, across tasks and across the motor fronto-BG circuits, we found beta (13-35 Hz) desynchronization and low-frequency oscillations (LFOs, <8 Hz) synchronization, which were locked to the movement cue. By contrast, at the time of the stop signal there were beta activations within the rIFG, STN, and GP. Importantly, successfully stopping seemed to link to a stop signal occurring prior to reaching the peak of beta desynchronization related to the initial movement cue. The other task, which required conflict processing, showed a different spectral patterns of LFOs, in BG and involved pre-SMA and SMA rather than rIFG.

Furthermore, there was coherence between BG and pre-SMA in this low-frequency range. **Conclusions**: Our work shows spectrally and spatially task-specific patterns of neural activation based on invasive neurophysiological recordings. These findings bear on the basic science of action regulation, and on the role of parallel long-range brain networks for action.

Disclosures: J. Choi: None. **M. Malekmohammadi:** None. **S. Niketeghad:** None. **A.R. Aron:** None. **U. Rutishauser:** None. **N. Pouratian:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.08/II16

Topic: E.03. Basal Ganglia

Support: NIMH Grant R01MH107797

Title: Coupling between cortical gamma and basal ganglia firing activity during selective upper limb control

Authors: *P. FISCHER[1,2], W. J. LIPSKI[3,4], W.-J. NEUMANN[5], P. FRIES[6], P. BROWN[1,2], M. RICHARDSON[7,8]
[1]Univ. of Oxford, Oxford, United Kingdom; [2]MRC Brain Network Dynamics Unit, Univ. of Oxford, Oxford, United Kingdom; [3]Ctr. for the Neural Basis of Cognition, Univ. of Pittsburgh, Pittsburgh, PA; [4]Brain Modulation Lab., Dept. of Neurolog. Surgery, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [5]Dept. of Neurol., Charité Univ. Med. Berlin, Berlin, Germany; [6]Ernst Struengmann Inst. (ESI), Frankfurt, Germany; [7]Dept. of Neurosurg., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [8]Univ. of Pittsburgh Brain Inst., Pittsburgh, PA

Abstract: Cortico-basal ganglia processing can be heavily affected in Parkinson's disease (PD), where neuronal communication that enables motor control gradually breaks down. LFP recordings from the human subthalamic nucleus (STN) suggest that 60-80 Hz gamma phase coupling between the STN and motor cortex may be important for movement initiation. To test if STN-spike-to-cortical-gamma phase coupling relates to selective activation of a contra- or ipsilateral effector and to motor performance, we analysed STN spike and cortical ECoG activity recorded in PD patients undergoing deep brain stimulation surgery. Patients performed a visually cued hand grip task with either the left or right hand. When gamma coupling was high already at the time of the GO cue, about 300ms before movement onset, reaction times were faster, consistent with a role in motor preparation. This relationship was only present for contralateral grip trials, where STN spikes were modulated in a specific pattern relative to the cortical gamma cycle. STN spikes phase-led cortical gamma fluctuations and thus may help to shape cortical gamma synchrony by temporally structuring inhibitory basal ganglia output. We also found that

the average cortical gamma phase coinciding with STN spikes was offset by half a cycle during ipsilateral compared to contralateral gripping. This may be a mechanism that contributes to selective contralateral limb control while other effectors remain still. The same cells were also coupled to cortical beta oscillations after movement completion, which provides evidence that neurons may be dynamically entrained to more than one rhythm as a task unfolds. Movement-related gamma coupling was present irrespective of whether cells increased or decreased their firing rates with movement or remained stable in their firing. Thus, the temporal pattern of STN spikes with respect to cortical phase provides important information in interpreting basal ganglia function beyond average changes in firing rate. To understand the mechanisms that underlie basic basal ganglia input-to-output transformations, it will be key to perform multi-site recordings and analyse spike patterns relative to LFP oscillations in strictly controlled movement tasks.

Disclosures: P. Fischer: None. **W.J. Lipski:** None. **W. Neumann:** None. **P. Fries:** None. **P. Brown:** None. **M. Richardson:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.09/II17

Topic: E.03. Basal Ganglia

Support: MRC (MR/P012272/1 and MC_UU_12024/1)
Rosetrees Trust
National Institute of Health Research Oxford Biomedical Research Centre
Swiss Parkinson Association

Title: Electrophysiological correlate of Upper and Lower limb in the human basal ganglia

Authors: *G. TINKHAUSER[1], S. SHAH[1], K. PETERMAN[2], P. FISCHER[1], T. NYGYUEN[3], I. DEBOVE[2], A. NOWACKI[3], F. TORRECILLOS[1], S. KHAWALDEH[1], A. POGOSYAN[1], H. TAN[1], M. SCHUEPBACH[2], C. POLLO[3], P. BROWN[1]
[1]Univ. of Oxford, MRC Brain Network Dynamics Unit, Oxford, United Kingdom; [2]Dept. of Neurol., University Hospital Bern, Switzerland; [3]Dept. of Neurosurg., University Hospital Bern, Switzerland

Abstract: Background: Upper and lower limb somatotopy in the human sensorimotor system is well described in the cerebral cortex. However, cortical inputs to the basal ganglia are highly convergent. Is body part organisation lost or retained in this convergence?
Objective: Here we address the above question by recording directly for the subthalamic nucleus (STN) in patients with Parkinson's disease (PD) undergoing functional neurosurgery. Recordings

were made with the new generation of segmented “directional” DBS electrodes.
Method: Local field potentials were recorded from 8-contact directional DBS electrodes in 12 PD patients during repetitive contralateral and ipsilateral upper and lower limb movements. Movement-related spectral changes were estimated and compared between limbs. The spatial distributions of band-limited spectral changes were also estimated, aided by projection of the coordinates of the directional contacts in MNI space to give weighted probability density functions within the STN.
Results: Upper and lower limbs showed a striking difference in their movement-related beta desynchronization with greater involvement of the high beta band (21-35Hz) during lower limb movement, regardless of whether this was contralateral or ipsilateral to the nucleus and also independent of the strength of upper and lower limb movement. The spatial distribution of upper and lower limb movement related activities was similar in the beta (13-35Hz) frequency range.
Discussion: STN activities related to upper and lower limb movements are differentially expressed within the beta band. Given the relative lack of spatial discrimination between patterns of beta modulation related to upper and lower limb movements, the frequency difference may serve to help tag different activities in the frequency rather than spatial domain. Whether greater spatial differentiation between limb activities might be seen with higher resolution electrodes, at higher frequencies or in healthy subjects remains to be seen.
Conclusion: We provide evidence for the organisation of limb representations in the frequency domain within the STN. This information could be used to fine-tune the delivery of deep brain stimulation and to increase the potential information available from the STN for the control of neuroprostheses.

Disclosures: G. Tinkhauser: None. **S. Shah:** None. **K. Peterman:** None. **P. Fischer:** None. **T. Nygyuen:** None. **I. Debove:** None. **A. Nowacki:** None. **F. Torrecillos:** None. **S. Khawaldeh:** None. **A. Pogosyan:** None. **H. Tan:** None. **M. Schuepbach:** None. **C. Pollo:** None. **P. Brown:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.10/II18

Topic: E.03. Basal Ganglia

Title: Magnetothermal deep brain stimulation in freely moving mice

Authors: *S. HESCHAM[1], P.-H. CHIANG[2], J. MOON[2], M. CHRISTIANSEN[2,3], Y. TEMEL[1], P. ANIKEEVA[2]
[1]Maastricht Univ., Maastricht, Netherlands; [2]MIT, Cambridge, MA; [3]ETH Zürich, Zürich, Switzerland

Abstract: Deep brain stimulation (DBS) has long been used to alleviate symptoms in patients suffering from psychiatric and neurological disorders. Here, we demonstrate that a wireless magnetothermal approach to DBS can provide tetherless neuromodulation sufficient to evoke motor behavior in freely moving mice. Magnetothermal DBS exploits hysteretic heating of magnetic nanoparticles in the presence of an alternating magnetic field. Therefore, we heat-sensitized neurons in the subthalamic nucleus (STN) and premotor cortex (M2) by expressing the cation channel TRPV1. While magnetothermal stimulation in the M2 did not result in any difference in motor behavior, stimulation of the STN caused rotations around the body-axis. The duration of the behavior extended for 30 sec even after the alternating magnetic field was turned off. Immunohistochemical analysis revealed increased neural activity in the primary motor cortex for STN stimulated mice. This approach may provide attractive means to activate deep-brain circuits without the need for surgical implants and connectors.

Disclosures: S. Hescham: None. **P. Chiang:** None. **J. Moon:** None. **M. Christiansen:** None. **Y. Temel:** None. **P. Anikeeva:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.11/JJ1

Topic: E.03. Basal Ganglia

Support: MRC Grant MR/P012272/1
MRC Grant MC_UU_12024/1
Rosetrees Trust
NIH Research Oxford Biomedical Research Centre
Swiss Parkinson Association

Title: Timing and amplitude of beta bursts in the subthalamic nucleus predict single-trial motor performance

Authors: *F. TORRECILLOS[1,2], G. TINKHAUSER[1,2,3], P. FISCHER[1,2], A. GREEN[1], T. AZIZ[1], T. FOLTYNIE[4], P. LIMOUSIN[4], L. ZRINZO[4], K. ASHKAN[5], P. BROWN[1,2], H. TAN[1,2]
[1]Nuffield Dept. of Clin. Neurosciences, Oxford, United Kingdom; [2]MRC Brain Network Dynamics Unit, Oxford, United Kingdom; [3]Dept. of Neurol., Bern Univ. Hosp. and Univ. of Bern, Bern, Switzerland; [4]Unit of Functional Neurosurg., Sobell Dept. of Motor Neurosci. and Movement Disorders, London, United Kingdom; [5]Departments of Neurol. and Neurosurg., King's Col. Hosp., London, United Kingdom

Abstract: The movement-related modulation of beta band oscillations in the cortico-basal ganglia motor network is well established and suggests a role of these oscillations in voluntary

movement. However, most of the studies linking beta power to motor performances are based on data averaged across trials that ignore the fast dynamics of oscillatory activity and the trial-by-trial variability of motor responses. Recently it has become apparent that beta activity comes in transient bursts, which are prolonged in untreated patients with Parkinson's disease. Here, we test the hypothesis that the timing and amplitude of the bursts present in treated patients may help explain more physiological variations in motor behaviour at the single trial level. Local field potentials (LFP) were recorded from the subthalamic nucleus (STN) in twelve parkinsonian patients while they performed a visually cued joystick task. Patients were on medication, so that motor performance was optimised as far as possible. Beta bursts were defined as periods surpassing a threshold of the 75th percentile of the mean beta power. We found that beta bursts occurring in a time-limited window around the Go cue, well before movement onset, reduced the peak velocity of the subsequent movement and that this effect was further amplified by the amplitude of the beta burst. Additionally, prolonged reaction times were observed when bursts occurred immediately after the GO signal. Importantly, we confirmed that these behavioural effects were specifically related to the beta bursts and not secondary to beta power fluctuations, were limited to the STN contralateral to the active limb and confined to the beta frequency band. Together, these results suggest that the timing of beta bursts might serve to dynamically adapt moment-to-moment motor performance.

Disclosures: F. Torrecillos: None. **G. Tinkhauser:** None. **P. Fischer:** None. **A. Green:** None. **T. Aziz:** None. **T. Foltynie:** None. **P. Limousin:** None. **L. Zrinzo:** None. **K. Ashkan:** None. **P. Brown:** None. **H. Tan:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.12/JJ2

Topic: E.03. Basal Ganglia

Support: NIH/NINDS grant P50-NS098685
a grant from the NIH Office of Research Infrastructure Programs OD P51-OD011132
National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002378

Title: Optogenetic stimulation of thalamocortical projections alters cortical phase-amplitude coupling

Authors: *M. CAIOLA[1], A. GALVAN[2], T. WICHMANN[3]
[1]Yerkes Natl. Primate Res. Ctr., [2]Yerkes Natl. Primate Res. Ctr. and Dept. of Neurology, Sch. of M, Emory Univ., Atlanta, GA; [3]Dept Neurol, Emory Univ. Sch. Med., Atlanta, GA

Abstract: Studies of phase-amplitude coupling (PAC) have become popular to examine the coherence between the slow and fast oscillations of a recorded signal due to its offline computation capability and its ease to compute over a wide range of frequencies. Recently, the coupling of the amplitude of gamma band oscillations to the phase of alpha- or beta-range oscillations has been shown to increase in electrocorticogram (ECoG) signals recorded in parkinsonian patients and primates (compared to recordings in normal individuals or those with other diseases), leading many to believe that it may be suitable as a possible biomarker for the disease and its associated motor symptoms. The reasons for the cortical PAC changes are not clear, but it is likely that cortical PAC patterns are heavily dependent on thalamic efferents to the cerebral cortex. We studied this issue directly with a series of optogenetic experiments in Rhesus macaques.

In two animals, we virally transfected neurons in the basal ganglia receiving territory of the ventral motor thalamus to express the excitatory opsins C1V1 and Chronos. We then recorded ECoG signals from the primary motor cortex and the supplementary motor area during somatic (thalamic) or terminal (cortical) stimulation. We compared PAC during stimulation with single pulses or with trains of pulses of light stimulation with PAC results based on pre- or post-stimulation ECOG recordings, using the Kullback–Leibler divergence method of quantifying PAC. We found that optogenetic stimulation caused significant PAC in gamma amplitude during periods of light pulses. The effect of terminal stimulation was stronger than that of somatic stimulation of the thalamocortical projecting neurons. These results suggest that activation of thalamic inputs to the frontal cortex may result in a temporary entrainment of gamma oscillatory activity to oscillations at lower frequencies. Conceivably, such entrainment effects triggered by thalamic activation could, in part, explain the finding of globally altered PAC patterns in the parkinsonian state.

Acknowledgments: Supported by NIH/NINDS grant P50-NS098685 (Udall Center grant), a grant from the NIH Office of Research Infrastructure Programs OD P51-OD011132 to the Yerkes National Primate Research Center and in part by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002378.

Disclosures: M. Caiola: None. **A. Galvan:** None. **T. Wichmann:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.13/JJ3

Topic: E.03. Basal Ganglia

Support: NIH/NINDS grant P50-NS098685 (Udall Center grant)
NIH Office of Research Infrastructure Programs OD P51-OD011132 to the Yerkes National Primate Research Center

Title: Corticothalamic functional connectivity in healthy and parkinsonian (MPTP-treated) nonhuman primates: An optogenetic study

Authors: *D. ALBAUGH[1], Y. SMITH[3], A. GALVAN[2], T. WICHMANN[4]
[1]Yerkes Natl. Primate Res. Ctr., [2]Yerkes Natl. Primate Res. Ctr. and Dept. of Neurology, Sch. of M, Emory Univ., Atlanta, GA; [3]Yerkes Res. Ctr., Udall Ctr. Excel. For Parkinson's Dis. and Dept. of Neurol., Atlanta, GA; [4]Dept Neurol, Emory Univ. Sch. Med., Atlanta, GA

Abstract: While it can be expected that cortical inputs strongly impact the activity of thalamocortical projection neurons in the basal ganglia receiving territory of the motor thalamus (BGMT), the processing of cortical inputs within the primate BGMT is likely to be complex, as these inputs target both principal cells and inhibitory interneurons in the thalamus. In traditional models of the pathophysiology of Parkinson's Disease (PD) abnormal activity patterns within the basal ganglia alter the processing of the (otherwise normal) cortical inputs to the BGMT. Our anatomical data suggests, however, that the cortical projections to the BGMT may themselves be morphologically abnormal in the parkinsonian state. Compared to healthy controls, parkinsonian (MPTP-treated) nonhuman primates (NHPs) show a reduction in cortical inputs to BGMT. The purpose of this study is to directly compare the functional influence of activation of the motor corticothalamic pathway in NHPs on the electrophysiological activity of single BGMT neurons in the healthy and parkinsonian states (induced by exposure of the animals to MPTP). The study is conducted in Rhesus macaques because the anatomy of corticothalamic interactions and intrinsic BGMT anatomy in these animals is very similar to that found in humans, specifically including the presence of extensive numbers of BGMT interneurons (which are not present in rodents). To selectively stimulate corticothalamic terminals in the BGMT, we use an optogenetic approach, virally transducing deep-layer motor cortical neurons with excitatory opsins, and optically stimulating their terminals in the BGMT. In previous studies, we found that corticothalamic pathway stimulation elicits diverse responses among BGMT neurons, including inhibitions in nearly half of all responding neurons in normal animals. Here, we report preliminary results from two subjects in an ongoing study in which the animals are first studied in the normal state, and then be rendered parkinsonian using chronic, low-dose MPTP exposure. If, as expected, corticothalamic inputs contribute less to the shaping of BGMT output to the cortex, the influence of other BGMT afferents, including those from the basal ganglia, may proportionally gain in strength, contributing to the abnormal bursting and oscillatory patterns in BGMT neurons that we and others have previously demonstrated.

Disclosures: D. Albaugh: None. **Y. Smith:** None. **A. Galvan:** None. **T. Wichmann:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.14/JJ4

Topic: E.03. Basal Ganglia

Support: JSPS Grant-in-Aid for Scientific Research on Innovative Areas (15H05873)

Title: The chemogenetic suppression of the primate subthalamic nucleus impairs voluntary movements by disturbing the firing pattern in the internal segment of the globus pallidus

Authors: *T. HASEGAWA[1], S. CHIKEN[1,3], K. KOBAYASHI[2,3], A. NAMBU[1,2,3]
[1]Div. of Syst. Neurophysiol., [2]Sec of Viral Vector Develop., Natl. Inst. for Physiological Sci., Okazaki, Japan; [3]Dept of Physiol Sci., SOKENDAI, Okazaki, Japan

Abstract: The "rate model" of the basal ganglia (BG) functions proposes that the neuronal firing rate changes in the BG impair voluntary movements as seen in hemiballism, which is caused by lesions in the subthalamic nucleus (STN). The STN receives inputs from the cerebral cortex and the external segment of the globus pallidus and sends strong excitatory outputs to the internal segment of the globus pallidus (GPi), the output nucleus of the BG; STN lesions induce hemiballism presumably due to activity decrease in the GPi. To explore the neural mechanisms of this movement disorder, the Designer Receptors Exclusively Activated by Designer Drugs (DREADD) system was utilized to reversibly inhibit the STN activity.
We injected an adeno-associated viral vector expressing the inhibitory DREADD receptor, hM4Di, to the motor area in the STN of a male Japanese monkey (*Macaca fuscata*). The intravenous administration of 1.0 mg/kg BW of clozapine N-oxide (CNO) was performed 3-22 weeks after vector injection during a behavioral task and/or electrophysiological recordings. The STN multi-unit activity decreased by 50-55% in a few recording sites (2 out of 11) starting 15 min after the administration. This partial STN suppression induced abnormal involuntary movements on the contralateral upper limb. In addition, in a reaching task, hand movements became unstable, while the movement initiation timings were not affected.
The motor area of the GPi was electrophysiologically identified and single unit activity was recorded before and after the CNO administration (n = 19). The GPi neurons exhibited the excitation, inhibition, or mixed activity change during the reaching task. With the STN suppression, the baseline firing rates were not affected and the trial-averaged neuronal activity during movements was relatively unchanged in the GPi; however, the Fano factors and coefficient of variation, measures of the dispersion of spike trains, increased, ($P < 0.005$ and $P < 10^{-4}$, respectively) and the pauses, breaks in spike trains, became longer ($P < 0.001$). In summary, the suppression of the STN induces high variability in the spike trains in the GPi, which would cause aberrant movements and impair voluntary movements. Our results imply that the STN may dynamically modulate GPi activity to control on-going movements, contrary to the movement control through firing rates as proposed in the "rate model."

Disclosures: T. Hasegawa: None. **S. Chiken:** None. **K. Kobayashi:** None. **A. Nambu:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.15/JJ5

Topic: E.03. Basal Ganglia

Support: Grant-in-Aid for Scientific Research (15H05873) from the MEXT, Japan

Title: The impact of glutamatergic and GABAergic inputs to the subthalamic nucleus activity in monkey

Authors: *Z. POLYAKOVA[1,2], N. HATANAKA[1,2], S. CHIKEN[1,3], H. KITA[4], A. NAMBU[1,2]
[1]Div. Syst. Neurophysiol, Natl. Inst. Physiol Sci., Okazaki, Japan; [2]Dept Physiol Sci., SOKENDAI, Okazaki, Japan; [3]Dept Physiol Sci., Sokendai, Okazaki, Japan; [4]Dept Anat and Neurobiol, Univ. Tennessee Hlth. Sci. Cent, Memphis, TN

Abstract: The symptoms of basal ganglia (BG) disorders are linked to abnormal activity of the subthalamic nucleus (STN). Modulating STN activity by deep brain stimulation or surgical lesion is an effective treatment of movement disorders. The STN receives glutamatergic inputs directly from the cortex and GABAergic inputs from the external segment of the globus pallidus (GPe), which compose the cortico-STN *hyperdiret* and cortico-striato-GPe-STN *indirect* pathways, respectively. Then, the STN drives the internal segment of the globus pallidus, the output nucleus of the BG. Thus, it is important to clarify how STN neuronal activity is controlled by these inputs. In the present study, we performed STN neuronal recording in awake monkeys (*Macaca fuscata*). Electrical stimulation of the motor cortices induced bi-phasic response in STN neurons: early excitation (*e-ex*) and following late excitation (*l-ex*). To examine the origin of each response component, we performed local micro-injections of blockers in the vicinity of recorded STN neurons and blocker injections into the striatum or the GPe. Spontaneous neuronal activity and cortically induced neuronal responses were compared before and after drug application. The amplitude and duration of cortically evoked *e-ex* in the STN were decreased after local application of 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP, NMDA receptor antagonist). Local injection of 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX, AMPA-kainate receptor antagonist) decreased the amplitude of *l-ex*. Local application of mixture of NBQX and CPP into the STN decreased the amplitude and duration of *e-ex*, amplitude of *l-ex* and spontaneous firing rates. STN spontaneous firing rates increased in case of local gabazine ($GABA_A$ receptor antagonist) injection. The amplitude and duration of cortically evoked *l-ex* were decreased after muscimol ($GABA_A$ receptor agonist) injection into the striatum. Application of gabazine or muscimol into the GPe decreased the amplitude and duration of cortically evoked *l-ex*. Muscimol injection into the GPe increased STN spontaneous firing rates. Gabazine injection into the GPe decreased STN spontaneous firing rates and

increased burst index and coefficient of variation. These findings suggest that the bi-phasic response in the STN is mediated by the *hyperdirect* and *indirect* pathways, which causes *e-ex* and *l-ex*, respectively. The *hyperdirect* pathway is mainly mediated by NMDA receptors.

Disclosures: Z. Polyakova: None. **N. Hatanaka:** None. **S. Chiken:** None. **H. Kita:** None. **A. Nambu:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.16/JJ6

Topic: E.03. Basal Ganglia

Support: NIH R01-NS085188
P41 EB015894
P30 NS076408
University of Minnesota Udall center P50NS098573

Title: Influence of dbs lead model and brain shift on electrode position and bending of proximal lead: A high-resolution postoperative ct study

Authors: *J. NIEDERER[1], R. PATRIAT[1], R. R. SHAMIR[2], D. P. DARROW[3], M. C. PARK[3], L. E. SCHROCK[4], N. HAREL[1]
[1]Radiology, Univ. of Minnesota Twin Cities, Minneapolis, MN; [2]Surgical Information Sciences, Inc., Minneapolis, MN; [3]Dept. of Neurosurg., [4]Dept. of Neurol., Univ. of Minnesota, Minneapolis, MN

Abstract: Deep brain stimulation (DBS) is a neurosurgical treatment requiring the implantation of electrodes in deep target regions of the brain. Precise placement of the DBS electrode has been shown to be crucial for DBS success and optimal patient outcomes. Intracranial air (ICA) can accumulate between the cranium and the brain during surgery, causing movement of brain tissue relative to its natural anatomical position. The purpose of this study was to investigate ICA volumes following surgery and DBS lead model as potential factors affecting electrode tip migration and proximal lead bowing. ICA can be measured immediately following surgery and typically resolves within four weeks post-surgery. High-resolution postoperative CT scans (≤1.0 mm resolution in all directions) at 24 hours (24-hr) and 4-week-follow-up (4-wks) were acquired after 32 DBS surgical cases, in which six cases were bilateral surgeries. A total of 38 DBS leads (n=38) were available for analysis of ICA volume and electrode position. DBS leads included Boston Scientific Vercise, Abbott/St. Jude Medical Infinity (Abbott/SJM) and Medtronic 3389. ICA volume was measured within 24-hr postoperative and correlated with electrode tip displacement and radiographic measurements of proximal lead bowing at 4-wks postoperative

CT. A one-way ANCOVA test was used to model proximal lead bowing (mean±SD: 2.2±1.2 mm) as a function of DBS lead model, ICA volume (8760±984 mm^3), and the interaction between DBS lead model and ICA volume. DBS lead model ($F=8.7$, $df=2$, $p<0.001$) and ICA volume ($F=29.2$, $df=1$, $p<10^{-5}$) were found to be significant predictors of proximal lead bowing. A Tukey-Kramer post hoc test revealed that proximal lead bowing for the Medtronic 3389 DBS lead (2.9±1.2 mm) was significantly different from the Boston Scientific Vercise (2.0±1.1 mm, $p=0.008$) and Abbott/SJM Infinity DBS leads (1.7±0.6 mm, $p=0.001$) although the Vercise and Infinity DBS leads did not differ from one another. No significant relationship was observed between DBS lead model or ICA volume and electrode tip migration (1.1±0.5 mm). Though differences in proximal DBS lead bowing were observed between DBS lead models, electrode tip migration was not affected by ICA volume or bending of the DBS lead. This may indicate a potential stretching of the electrode around the location of maximum proximal lead bowing. The significant difference observed between the Medtronic 3389 electrode and Abbott/SJM Infinity and Boston Scientific Vercise electrodes may reflect hardware engineering subtleties in the construction of segmented (Abbott/SJM) and eight contact (Boston Scientific) electrodes compared to the Medtronic 3389 four contact electrode.

Disclosures: J. Niederer: None. **R. Patriat:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences, Inc.. F. Consulting Fees (e.g., advisory boards); Cardionomic, Inc.. **R.R. Shamir:** None. **D.P. Darrow:** None. **M.C. Park:** 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.; Medtronic, Inc., Boston Scientific, Advanced Neuromodulation Systems, Inc. - St. Jude Medical, St. Jude Medical. F. Consulting Fees (e.g., advisory boards); Zimmer Biomet, SmartImplantSystems, Inc.. **L.E. Schrock:** None. **N. Harel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences, Inc..

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.17/JJ7

Topic: E.03. Basal Ganglia

Support: Dinapoli Parkinson's Disease Research Fund

Title: Deep brain stimulation at the interface of ventroanterior and ventrolateral nuclei of the thalamus as a novel effective neuromodulatory approach for Parkinson’s disease

Authors: *H. R. TUCKER[1], E. MAHONEY[1], A. CHETRI[1], G. KIM[1], A. AUDIL[1], B. MOOLICK[1], E. MOLHO[2], J. G. PILITSIS[1], D. SHIN[1]
[1]Neurosci. & Exptl. Therapeut., [2]Neurol., Albany Med. Col., Albany, NY

Abstract: The gold standard treatment for Parkinson's disease is the levodopa. However, long-term use can cause disabling abnormal movements called dyskinesias. An alternative treatment option is deep brain stimulation (DBS). The two FDA-approved DBS targets for PD are the subthalamic nucleus (STN) and globus pallidus pars interna (GPi). Both approaches improve quality of life and motor scores by ~50-70% in well-selected patients, but can also elicit adverse effects on cognition and other non-motor symptoms. Therefore, identifying a novel DBS target having greater and more expansive therapeutic efficacy for patients not optimally responsive to current targets with fewer side-effects has clear clinical merit.
A plausible DBS target is the ventroanterior (VA) and ventrolateral (VL) nuclei of the thalamus (VA+VL). Despite being critically positioned in the basal ganglia-thalamic-cortical motor loop, the VA+VL thalamus has been largely ignored as a DBS candidate in the clinical and preclinical research domains. We aim to be the first to investigate this notion.
After optimization, we noted that 10 Hz, 100 µsec pulse width and 100 µA cathodic bipolar stimulation improved forelimb akinesia in hemiparkinsonian rats.
Specifically, they touched with their left impaired forepaw 6.5% prior to DBS, but 51.4% with VA+VL DBS. Electrical stimulation of the space between the VA and VL caused higher spiking frequency in VL neurons, transition from evoked burst APs to many single spikes and presence of large depolarizing potentials. In conclusion, VA+VL can serve as an effective DBS target for treatment of PD akinesia by altering thalamic neuronal spike frequency and pattern.

Disclosures: H.R. Tucker: None. **E. Mahoney:** None. **A. Chetri:** None. **G. Kim:** None. **A. Audil:** None. **B. Moolick:** None. **E. Molho:** None. **J.G. Pilitsis:** None. **D. Shin:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.18/JJ8

Topic: G.02. Motivation

Support: Donders Institute Top Talent 2014
Dutch Brain Foundation Grant F2013(1)-15 to R.H

Title: Effects of dopaminergic medication on choice bias in Parkinson's disease

Authors: *A. J. VAN NULAND[1], R. C. HELMICH[2,1], I. TONI[1], R. COOLS[1], H. E. M. DEN OUDEN[1]

[1]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ., Nijmegen, Netherlands; [2]Dept. of Neurol., Radboud Univ. Med. Ctr., Nijmegen, Netherlands

Abstract: Bradykinesia, rigidity and resting tremor are core symptoms of Parkinson's Disease (PD), and are relieved by dopaminergic medication. However, many patients also show cognitive and motivational dysfunction. We see that PD patients have an increased ability to learn from aversive outcomes, that is reversed by dopaminergic medication, leading to preferential learning from rewards (Cools 2006). More recent ideas have posited a role of dopamine in the interaction between these processes in the form of motivational biases in motor activation (Frank 2004). Here we test this in PD patients, where we hypothesized that dopaminergic medication may alter this interaction.

Our second question concerns the large heterogeneity in PD. Specifically, we see that patients without tremor show more cognitive decline (Jankovic 2011), higher substantia nigra (SN) degradation (post mortem studies, Jellinger 1992), and reduced DAT binding in the striatum (Helmich 2011) compared with tremor-dominant patients; suggesting differences in their cognitive and motivational dysfunction. Accordingly, we hypothesized the effects of dopaminergic medication on reward and punishment learning to differ between tremor-dominant and non-tremor patients.

We included 60 patients with idiopathic PD without severe cognitive dysfunction; 40 tremor-dominant, 20 non-tremor patients and 20 controls. Patients were measured in pseudorandomized order, both OFF and ON dopaminergic medication (200/50 mg of levodopa-benserazide-dispers). In both sessions, participants performed a reinforcement learning task to disentangle the separate but interacting axes of motor response requirement (Go/NoGo) and motivational valence (reward/punishment). We investigated the effect of dopamine (OFF vs. ON) on choice and response speed.

Due to test-retest bias, we restricted analysis to session one. Contrary to our expectations, we found no overall effect of medication on motor or motivational processing, nor their interaction. However, there was a significant effect of PD group on the interaction between medication and valence: Non-tremor patients behaved as expected, performing better for reward trials ON medication, while tremor-dominant patients showed declined punishment learning OFF medication. This was independent of the motor response domain. This finding suggests that effects of dopaminergic medication on reward sensitivity are modulated by the Parkinson phenotype (tremor-dominant or non-tremor), which may be related to differences in cognitive decline between these groups, and potentially, differences in SN degradation, underlining the diversity of disease expression in PD.

Disclosures: A.J. Van Nuland: None. **R.C. Helmich:** None. **I. Toni:** None. **R. Cools:** None. **H.E.M. Den Ouden:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.19/KK1

Topic: E.03. Basal Ganglia

Support: NINDS K08
Parkinsons Disease Foundation
NINDS F31

Title: Aberrant striatal activity in parkinsonism and levodopa-induced dyskinesia

Authors: *M. RYAN[1], C. BAIR-MARSHALL[2], A. B. NELSON[2]
[1]UC San Francisco, San Francisco, CA; [2]Neurol., UCSF, San Francisco, CA

Abstract: In Parkinson's Disease (PD), the loss of dopaminergic input profoundly alters the activity of the striatum, the input nucleus of the basal ganglia. The mainstay treatment for PD, levodopa, relieves many of the motor symptoms of the disease, but long-term treatment is often complicated by the development of involuntary movements, known as levodopa-induced dyskinesia (LID). While the mechanisms underlying PD and LID are currently unknown, aberrant firing of striatal neurons is response to chronic dopamine loss and dopamine replacement therapy is a prevailing hypothesis. Using single-unit recordings of optically identified direct and indirect pathway neurons in a mouse model of PD and LID, we sought to dissect the responses of striatal neurons to chronic and acute changes in dopamine. Using this approach, we found that dopamine loss was associated with a profound loss of direct pathway firing, while levodopa robustly modulated both direct and indirect pathway neuron firing beyond rates typically observed in healthy controls. Both direct and indirect pathway neurons also exhibited impaired correlations to movement following dopamine loss, which was not restored by levodopa. Finally, we identified a distinct subpopulation of direct pathway neurons which showed aberrant excitation in response to levodopa, with firing rates tightly correlated to dyskinesia.

Disclosures: M. Ryan: None. **C. Bair-Marshall:** None. **A.B. Nelson:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.20/DP07/KK2

Topic: E.03. Basal Ganglia

Title: Massively sparse coding of dynamics in basal ganglia

Authors: *T. D. SANGER
Biomed. Engin., USC, Los Angeles, CA

Abstract: Deep-brain stimulation surgery provides an opportunity for single-unit recording in the basal ganglia and thalamus of humans. Firing rates in the internal globus pallidus (GPi) of adults with Parkinson's disease and in non-human primates are typically 40hz or greater. In GPi and thalamus of children with dystonia due to cerebral palsy (CP), we find firing rates are typically 5-10hz, and there is a large subpopulation of slow-firing cells with rates less than 1hz. Simultaneous firing (within 0.5msec) is counted for all pairs of neurons and compared to the predicted rate for independent firing. The chi-squared statistic for autocorrelation between different cells is highly significant. The pattern indicates that coincident spikes occur much more frequently within the same region, and are seen most often in GPi, Voa/Vop, and STN. Significant coincidence at 0 delay suggests that simultaneous spikes are due to common inputs to each region. These findings are consistent with a digital hash code, in which sensory-motor events are encoded in time-locked patterns of firing. There are approximately 350,000 neurons in each human GPi [Hardman et. al. 2002], sufficient to allocate 50 two-neuron pairs for every second, and 17 three-neuron triplets for every millisecond of an 80-year life. This supports an algorithm in which all experience is stored, and learning (through dopamin- ergic systems) identifies which experiences are rewarded and selected for future repetition. Generalization is predicted to occur only after sufficient repetitive practice of similar senso- rimotor tasks, so that variability is experienced and learned. The structure is consistent with common observations of motor learning, including highly context-specific generalization, "one- shot" learning, minimal interference between dissimilar tasks, and absence of forgetting. I provide simulations of a spike-based persistent memory algorithm for robot control that reflects the human recordings and possesses these properties.

Disclosures: T.D. Sanger: None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.21/KK3

Topic: E.03. Basal Ganglia

Support: Ministry of Science and Technology Taiwan 106-2917-I-564-027
MRC Grant MR/P012272/1
MRC Grant MC_UU_12024/1

Title: Identifying gait dysfunction in Parkinson's disease using local field potentials

Authors: C.-H. YEH[1], P. FISCHER[1], C.-C. CHEN[2], *H. TAN[1], P. BROWN[1]
[1]Univ. of Oxford, Oxford, United Kingdom; [2]Chang Gung Mem. Hosp., Taoyuan, Taiwan

Abstract: Parkinson's disease (PD) is characterized by several motor signs. Standard deep brain stimulation (DBS) of the subthalamic nucleus (STN) treats rigidity, bradykinesia and tremor, but can fail to improve freezing of gait (FOG). This has prompted trials of alternative stimulation patterns and brain sites. An ideal approach might be to automatically switch between stimulation regimes according to need. We set out to identify periods of increased risk of FOG from local field potentials (LFP) recorded directly from the DBS electrode so as to keep invasive or peripheral instrumentation to a minimum in any chronic realization of adaptive DBS. Recordings took place off dopaminergic therapy, in the interval between electrode implantation in STN and connection to a subcutaneously placed stimulating device a few days later. LFPs were recorded bilaterally (15 patients, 30 STNs), together with the signal from a triaxial accelerometer (ACC) fixed over the upper thoracic level spinous processes to record trunk acceleration. Two conditions, simple walking and dual task gait (walking and simultaneous performance of either a calculation, color Stroop or spatial memory task) were tested. Total power and the FOG index (iFOG) derived from the ACC were used to identify standing, walking and periods of increased risk of FOG. As expected, iFOG was higher during dual task gait. LFP β power was significantly higher during walking when iFOG was low, and higher still during standing. In addition, alpha power was elevated during dual task gait, and β power variability and the fractal α value over θ to α frequencies were highest during walking with a high iFOG (all $p<0.05$ in ANOVAs and post-hoc testing). The α/β power ratio, β power variability and fractal values were positively correlated, whereas β power was negatively correlated with iFOG across the different tasks (mean $r=0.34\pm0.04$, 0.22 ± 0.04, 0.22 ± 0.06 and -0.30 ± 0.06, respectively). The data suggest that it might be possible to decode iFOG and therefore risk of FOG from STN LFP recordings. Other than avoiding peripheral instrumentation, the LFP potentially offers the opportunity for early prediction. To explore this and to confirm the feasibility of closed-loop DBS for gait dysfunction, a Wiener cascade model was used to decode iFOG based on STN LFP using the

above features. Weight distribution across the features indicated that the α/β power ratio contributed most to decoding vulnerable gait periods. Critically, this contribution began 0.4s and peaked 0.1s before iFOG changes, potentially allowing anticipatory stimulation regime switching.

Disclosures: C. Yeh: None. **P. Fischer:** None. **C. Chen:** None. **H. Tan:** None. **P. Brown:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.22/KK4

Topic: E.03. Basal Ganglia

Support: University of Toronto
Canadian Research Chair Tier I

Title: Motor synchronization to rhythmic auditory stimulation (RAS) attenuates dopamine responses in the ventral striatum in young healthy adults

Authors: *Y. KOSHIMORI[1,3], A. STRAFELLA[2,3,4,5], M. VALLI[2,5], V. SHARMA[1], S.-S. CHO[3], S. HOULE[3], M. THAUT[1,3]
[1]Music and Hlth. Res. Collaboratory, [2]Inst. of Med. Sci., Univ. of Toronto, Toronto, ON, Canada; [3]Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada; [4]Toronto Western Hosp., Toronto, ON, Canada; [5]Krembil Res. Inst., Toronto, ON, Canada

Abstract: Objective and rationale: External auditory stimuli such as metronome clicks and rhythmic beats in music facilitate motor behaviors in healthy adults and clinical populations such as people with Parkinson's disease (PD).[1,2] Auditory-motor entrainment modulates activities in the basal ganglia (BG).[3,4] However, the exact underlying neurochemical mechanisms of dopamine (DA) are entirely unknown. The current study is sought to investigate the role of DA in BG during rhythmic entrainment in young healthy adults. **Methods**: Eleven (M:5) right-handed young healthy adults aged between 18 and 35 were included in this study. Each participant underwent two [^{11}C]-(+)-PHNO-PET scans. During one PET scan, a participant performed a finger tapping task synchronized to RAS with different tempi (RAS condition). During the other scan, he/she performed the same finger tapping task without RAS (No-RAS condition). The PET images were processed using the in-house software platform and binding potential relative to the non-displaceable compartment (BP_{ND}) values were used as outcome measures for DA responses and derived using the simplified reference tissue method using PMOD. DA responses were compared between conditions in the BG structures including the ventral striatum, putamen, caudate and globus pallidus bilaterally. **Results**: RAS reduced the

absolute tapping period error (p = 0.077) and significantly reduced tapping variability (p = 0.034). Nine of the 11 participants showed reduced DA responses during the RAS condition in the left ventral striatum (VS) compared to the No-RAS condition (p = 0.035). In addition, the DA responses in the left VS showed a significantly positive correlation with the DA responses in the left globus pallidus during the No-RAS condition (p = 0.026), which was not observed during the RAS condition. Additionally, using the [^{11}C]-(+)-PHNO data with partial volume correction, eight of the 11 participants showed greater DA responses during the RAS condition in the right VS compared to the No-RAS condition. **Conclusions and future directions**: Our data have corroborated that RAS facilitates motor behavior and demonstrated that RAS attenuates DA responses in the left VS in young healthy adults, suggesting that finger tapping without RAS may require more motivational/attentional effort to perform the task. The future studies will investigate whether RAS has the similar effect on DA responses in healthy older adults and people with PD who have altered DA systems. 1.Thaut et al (1996). Mov. Disord; 2. Thaut & McIntosh (1999). Care Manag J.; 3. Grahn & Brett (2007). J Cogn Neurosci; 4. McIntosh et al (1997). J Neurol Neurosurg Psychiatry.

Disclosures: Y. Koshimori: None. **A. Strafella:** None. **M. Valli:** None. **V. Sharma:** None. **S. Cho:** None. **S. Houle:** None. **M. Thaut:** None.

Poster

670. Observing and Altering Basal Ganglia Activity From Mouse to Human

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 670.23/KK5

Topic: E.03. Basal Ganglia

Support: Boettcher Foundation

Title: Human spike recordings acquired in the context of an open-source, intraoperative paradigm

Authors: *J. A. THOMPSON[1], G. FELSEN[2], S. OJEMANN[1], A. ABOSCH[1], A. TEKRIWAL[2]
[1]Neurosurg., [2]Dept. of Physiol. and Biophysics, Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Neurosurgical interventions that use active patient feedback, such as the implantation of a deep brain stimulating electrode, create an opportunity to conduct human behavioral experiments during the acquisition of invasive neurophysiology. Here, we present a modular, inexpensive system for auditory decision-making tasks, including stimulus presentation and collection of motor responses. We characterize behavioral responses with latency to respond and accuracy of response. In addition, we analyze the temporal pattern of substantia nigra pars reticulata (SNr) spiking relative to specific task events. We validate a decision-making task designed for use in the intraoperative setting. We have created an auditory-stimulus guided, two-

alternative forced choice (2AFC) task using the PsychToolBox suite developed in Matlab. Task responses are collected using an Arduino based single-hand held controller that has been customized with a 3D printed attachment. Neural activity is recorded from microelectrodes via a NeuroOmega system (Alpha Omega, Alpharetta GA). Task and neural data are aligned according to TTL signals sent from DATAPixx (VPixx Technologies, Montreal, Quebec), triggered by Matlab. We demonstrate the utility of a simple-to-implement sensory-motor task amenable to an intraoperative setting that can be combined with invasive neurophysiology. Data collected and analyzed to date demonstrates that single-unit activity reflects task variables associated with our 2AFC. For very low cost and minimal effort, most clinical neural recording system can be adapted for concurrent intraoperative behavioral testing using our framework. Barriers to conducting intraoperative electrophysiological studies in awake behaving human subjects remain high, but our work should significantly decrease the effort needed to implement a system with rich recording capabilities.

Disclosures: J.A. Thompson: None. **G. Felsen:** None. **S. Ojemann:** None. **A. Abosch:** None. **A. Tekriwal:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.01/KK6

Topic: E.04. Voluntary Movements

Support: NIH Grant R01-AG-031769

Title: Control of dynamic force tasks: Low-frequency oscillations in force and modulation of muscle activity

Authors: *S. PARK, C. KIM, B. YACOUBI KEYHANI, E. A. CHRISTOU
Applied Physiol. and Kinesiology, Univ. of Florida, Gainesville, FL

Abstract: Force variability during steady force tasks is strongly related to low-frequency oscillations (<0.25 Hz) in force. However, it is unknown whether low-frequency oscillations also contribute to the variability of dynamic force tasks. To address this, twelve healthy young participants (21.08 ± 2.99 years, 6 females) performed a sinusoidal force task at 15% MVC at two different frequencies (0.5 and 1 Hz) with isometric abduction of the index finger. We recorded the force from the index finger and surface EMG from the first dorsal interosseous muscle and quantified the following outcomes: 1) trajectory variability and accuracy; 2) power spectrum of force and EMG bursting below 2 Hz; 3) power spectrum of the interference EMG from 4-60 Hz. The trajectory variability and error significantly increased from 0.5 to 1 Hz task ($P < 0.01$). Increased force oscillations <0.25 Hz contributed to greater trajectory variability and

error for both the 0.5 and 1 Hz sinusoidal task ($R^2 > 0.33$; $P < 0.05$). The <0.25 Hz oscillations in force were positively associated with greater power in the <0.25 Hz for EMG bursting ($R^2 > 0.52$; $P < 0.01$). The modulation of the interference EMG from 35-60 Hz was a good predictor of the <0.25 Hz force oscillations for both the 0.5 Hz task and 1 Hz task ($R^2 > 0.66$; $P < 0.01$). These results provide novel evidence that, similar to steady contractions, low-frequency oscillations of the motor neuron pool appear to be a significant mechanism that controls force during dynamic tasks.

Disclosures: S. Park: None. **C. Kim:** None. **B. Yacoubi Keyhani:** None. **E.A. Christou:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.02/KK7

Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI

Title: Influence of transcranial static magnetic field stimulation over primary motor cortex on pinching force control

Authors: *K. NAKAGAWA[1,2,3], K. NAKAZAWA[1]
[1]Grad. Sch. of Arts and Sci., The Univ. of Tokyo, Tokyo, Japan; [2]Japan Society for the Promotion of Sci., Tokyo, Japan; [3]Toronto Rehabil. Inst., Toronto, ON, Canada

Abstract: Transcranial static magnetic field stimulation (tSMS) has recently been demonstrated to modulate cortical excitability (Oliviero et al. 2011; Kirimoto et al. 2014; Nojima et al. 2015) and sensory function (Gonzaletz-Rosa et al. 2015; Carrasco-Lopez et al. 2017) for human, but the effect of tSMS on motor behavior is still unknown. This study was performed to investigate whether tSMS on primary motor cortex (M1) can alter voluntary force control. Fourteen able-bodied subjects performed ballistic pinching contractions with predetermined submaximal force level without visual feedback. Tasks were performed in bilateral hands alternatively, before, 5 mini, 10 min after start of the intervention, immediately and 5 min after the end of intervention. A compact magnet for tSMS and a stainless steel cylinder for sham stimulation were positioned on either right or left M1 for 15 minutes. Results demonstrated that there was no difference between hands in mean force output level. However, we found significant differences in absolute error to the target force level between tSMS and sham conditioned hands during and after intervention, while there was no differences between right and left hands. Compared to the pre-intervention session, the absolute error increased in tSMS-conditioned hand, but not in sham-conditioned hand. These results suggested that perceptive or planning function in M1 rather than

final descending output function would be impaired in tSMS. In conclusion, tSMS on M1 can impair the accuracy of submaximal pinching force control.

Disclosures: K. Nakagawa: None. **K. Nakazawa:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.03/KK8

Topic: E.04. Voluntary Movements

Title: Motor cortical excitability was modulated after strong voluntary contraction

Authors: *W. DAI[1], K. KATO[2], J. ZHANG[3], K. KANOSUE[2]
[1]Grad. Sch. of Sport Sci., Waseda Univ., Tokorozawa, Saitama, Japan; [2]Fuculty of Sport Sciences, Waseda Univ., Saitama, Japan; [3]Sch. of kinesiology, Shanghai Univ. of Sport, Shanghai, China

Abstract: Motor learning facilitates motor cortical excitability through long-term potentiation (LTP). However, a single session involving a simple muscle contraction can also enhance motor cortical excitability. It is not yet clear whether the mechanisms that underlie the two phenomena are the same. This research examines whether changes in cortical excitability after a single session of simple muscle contraction are related to excitability changes that are produced by paired associative stimulation (PAS), which is known to elicit LTP. Eleven healthy subjects performed three types of rapid voluntary thumb contraction 90 times at 0.2Hz. In the "comfortable" task (T-C), the subjects were only required to flex their thumb as quickly as possible. In the "strong" task (T-S), the subjects were required to flex their thumb at 65%-85% of maximum voluntary contraction as measured by electromyography (EMG). In the "comfortable but control" task (T-CC), subjects were required to control the EMG level of thumb contraction at the same level as in the T-C task. The target EMG levels were viewed by the subjects on a computer screen. In the separate PAS experiment, repetitive pairing of median nerve stimulation and transcranial magnetic stimulation (TMS) over the contralateral motor cortex with a 25ms latency was applied 90 times at 0.2Hz to induce LTP (PAS25). Motor cortical excitability was measured with motor-evoked potentials (MEP) using TMS. We utilized a 1 mV MEP intensity baseline for each subject and stimulated with the same intensity at 0, 5, 10, 15, 20, 25, 30, 45, and 60 min after executing one of the three tasks or the PAS25. The average EMG level for T-C was significantly lower than that of T-S but was not different from T-CC. MEP amplitudes increased over time for both
PAS25 and T-S with a very similar time course. Among the three contraction tasks, only the peak value of T-S had a significant positive relationship with both the under-curve area (AUC) and the peak value of PAS25. Thus, it might be that the MEP modulation similar to that observed

in PAS25 occurred only in the T-S, in which strong contraction should be controlled. Thus, for MEP modulation, the crucial factor in the correspondence between PAS and a single session of simple muscle contraction involves the subject's voluntary control over a strong muscle contraction.

Disclosures: W. Dai: None. **K. Kato:** None. **J. Zhang:** None. **K. Kanosue:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.04/KK9

Topic: E.04. Voluntary Movements

Support: Marie Skłodowska-Curie Action

Title: Rapid learning and unlearning of sensory delays in self-touch

Authors: *K. KILTENI, C. HOUBORG, H. EHRSSON
Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: Prevalent theories of motor control posit that our brain uses internal models to predict the sensory consequences of our voluntary movements. Due to these predictions, the perception of the sensory feedback of our movements is attenuated compared to unpredictable stimuli of external origin and same intensity. It has previously been shown that these predictions are time-locked to our movements and even small delays between the movement onset and the sensory feedback can significantly reduce the attenuation of the latter. Here we test whether the brain can learn to predict a new temporal relationship between movement and somatosensory feedback.
A total of ninety volunteers participated in three experiments. All experiments included the same force discrimination task, in which the participants were asked to press a sensor with their right index finger that delivered a tap (2 N) on their left index finger. The tap was applied either immediately (0 ms) or with a 100 ms delay. Thereafter, a second tap (between 1 and 3 N) was applied on the left index finger and participants had to indicate which tap felt stronger using a foot pedal. Prior to the force discrimination task, participants were repeatedly exposed to either a 0 ms or a 100 ms delay between the press of the right index finger and a tap on the left index finger in a training session consisting of 50 (Experiment 1), 200 (Experiment 2) or 500 exposure trials (Experiment 3).
In Experiment 1 (50 exposure trials), we found a reduction in the participants' attenuation of immediate touch **(**N=30, $t(29)=2.86$, $p=0.008$**)** but no attenuation of the delayed touch (N=30, $t(29)=-1.23$, $p=0.231$). When including 200 exposure trials (Experiment 2), the new set of participants showed again a reduced attenuation of immediate touch (N=30, $t(29)=4.73$, $p<0.001$) but also exhibited an increased attenuation of the delayed touch (N=30, $t(29)=-2.65$, $p=0.013$).

With 500 exposure trials (Experiment 3) we found the same pattern with the new set of participants: decreased attenuation of immediate touch (N=30, t(29)=3.03, p=0.005), and increased attenuation of delayed touch (N=30, t(29)=-3.5156, p=0.002). We further observed that the reduction in the attenuation of immediate touch was correlated with the increase in the attenuation of delayed touch **(***r*=0.473, *t*(28)=2.84, *p*=0.008**)**. Taken together, the data from all three experiments consistently show that participants can rapidly learn and unlearn sensory feedback delays in their movements. These findings suggest that the brain can update the internal forward models by recalibrating the temporal relationship between our movements and their sensory consequences.

Disclosures: K. Kilteni: None. **C. Houborg:** None. **H. Ehrsson:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.05/KK10

Topic: E.04. Voluntary Movements

Title: Action observation suppresses I-waves in a muscle specific manner

Authors: *A. CRETU[1], N. WENDEROTH[2]
[1]Health, Sci. and Technol., Neural Control of Movement Lab., Zürich, Switzerland; [2]Neural Control of Movement Lab, ETH Zurich, Zurich, Switzerland

Abstract: Studies using single-pulse transcranial magnetic stimulation (spTMS) demonstrated that corticospinal excitability changes during action observation are similar to those obtained during action execution (i.e., motor resonance). However, the amplitude of motor evoked potentials (MEPs) elicited by spTMS reflects a combination of excitatory and inhibitory inputs which converge onto descending pyramidal tract neurons. It is unclear which of these components contribute to the muscle-specific modulation of M1 during action observation. One theory proposes that the late excitatory inputs to M1 come from premotor cortex which is one main node of the action observation network.
Here, we explored the modulation of early and late excitatory indirect inputs to M1 (I-waves) during action observation by employing a short intracortical facilitation (SICF) TMS protocol whereby suprathreshold TMS is followed by a subthreshold pulse which is separated by 1.3, 2.5 or 4.1 ms i.e., targeting the first (I1), second (I2) or third (I3) I-wave.
We measured changes in MEP amplitude in the index (FDI) and little finger (ADM) while participants observed snapshots from videos depicting the grasping of a jar using either a whole-hand (WHG) or precision grasp (PG). We used a succession of the three snapshots (reach, grasp, lift) which gave the impression of a continuous movement. TMS pulses were administered 200ms after grasp presentation since previous electrophysiological and TMS research showed

that motor resonance can be observed around 200ms after action onset.
We first tested whether motor resonance was present during the observation of grasp snapshots by assessing the muscle specificity elicited by spTMS during the observation of WHG and PG actions. We found a higher MEP amplitude in the ADM muscle when observing whole-hand versus precision grasping and the reversed result pattern for the FDI (revealed by significant muscle specificity p=.001).
Next we calculated the amplitude of the I-waves as the ratio between the average amplitude of MEP evoked by paired-pulse TMS and the average amplitude of the single-pulse MEPs, separately for each muscle, grasp type and paired-pulse protocol. Here, we found a grasp type x muscle specificity interaction which reached significance for the I2-wave (p=.023). Interestingly, the modulation pattern is reversed compared to the one obtained with single pulse, i.e. the I2-wave amplitude is higher during precision than whole-hand grip in the ADM muscle. We hypothesize that this apparent suppression of facilitation might be required for the inhibition of overt movements in the observer.

Disclosures: A. Cretu: None. **N. Wenderoth:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.06/KK11

Topic: E.04. Voluntary Movements

Support: Grant-in-Aid for Young Scientists (B) (16K16429)

Title: Modulation of capacity for motor learning by transcranial alternating current stimulation

Authors: *H. SUGATA[1], K. YAGI[2], S. YAZAWA[3], Y. NAGASE[4], K. TSURUTA[3], T. IKEDA[5], K. MATSUSHITA[6], K. KAWAKAMI[1]
[1]Fac. of Welfare and Hlth. Sci., Oita Univ., Oita, Japan; [2]Dept. of Clin. Laboratpry, [3]Dept. of Neurol., [4]Dept. of Rehabil., Junwakai Mem. Hosp., Miyazaki, Japan; [5]Res. Ctr. for Child Mental Develop., Kanazawa Univ., Kanazawa, Japan; [6]Dept. of Mechanical Engin., Gifu Univ., Gifu, Japan

Abstract: Transcranial alternating current stimulation (tACS) is a non-invasive brain stimulation technique that can facilitate motor learning. Although many tACS studies have focused on immediate motor performance or retention of motor learning by stimulation at 10, 20, and 70 Hz, few studies have examined the effect of tACS on the modulation of the capacity for motor learning. Considering that tACS affects motor performance, it may increase the capacity for motor learning. To resolve this issue, we investigated the capacity for motor learning before and after tACS. In addition, to clarify the brain activity during motor learning, we examined

oscillatory neural activity with magnetoencephalography (MEG) before and after tACS. Fifty-five healthy volunteers participated in this study. By means of a between-subject design, participants were randomly assigned to four stimulation groups (10 Hz, 20 Hz, 70 Hz, or sham). The subjects performed a visually cued button press motor learning task before and after tACS. MEG measurements were performed using a 306-channel whole-head MEG system during the motor learning task in a magnetically shielded room. After the initial motor learning task, tACS was delivered with a battery-driven constant current stimulator through a pair of saline-soaked sponge electrodes. The target and reference electrodes were placed over the C3 and right orbita, respectively. Stimulation was applied for 10 min at 1 mA. Impedance values were maintained below 10 kΩ. The results showed that there was a significant increase in the capacity for motor learning after 70 Hz tACS compared with that after sham stimulation ($p < 0.05$). In addition, MEG analysis showed a significant increase in beta band power after 70-Hz tACS ($p < 0.05$), but not in the other stimulation groups. Recent studies have reported that 70-Hz tACS over M1 facilitates force generation and movement velocity. In the present study, the capacity for motor learning significantly increased in the 70-Hz tACS group compared with that in the sham group. Furthermore, beta band cross frequency modulation was observed in the 70-Hz tACS group. Our results suggested that 70-Hz tACS increases the capacity for motor learning by cross-modulating beta oscillatory activity.

Disclosures: H. Sugata: None. **K. Yagi:** None. **S. Yazawa:** None. **Y. Nagase:** None. **K. Tsuruta:** None. **T. Ikeda:** None. **K. Matsushita:** None. **K. Kawakami:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.07/KK12

Topic: E.04. Voluntary Movements

Support: UTexas OUR Grant

Title: Digit force magnitude and inter-digit force coordination effects on performance of a complex isometric pinch force tracking task

Authors: J. VINES[1], M. SCHLEICHER[1], R. ADLIS[2], D. LEE[3], C. HILTON[1], R. T. EAKIN[1], *L. D. ABRAHAM[1]
[1]Kinesiology and Hlth. Educ., Univ. of Texas at Austin, Austin, TX; [2]Neurosci., [3]Biol., The Univ. of Texas at Austin, Austin, TX

Abstract: This study investigated how different required force levels and digit coordination patterns affect performance on a complex isometric pinch force tracking task. Forty-eight healthy volunteers (24 females, 24 males) ages 18-30 years (mean = 20.8 +/- 2.7) manipulated a cursor

with their right thumb and index finger pinch forces to track a target traveling counterclockwise around a square diamond path. Accuracy and error variability were compared across four different force-level diamond paths. Each path required continuous simultaneous but independent changes in the patterns of force application and release by the thumb and index finger. Participants were pseudo-randomly assigned to a practice order so that two were assigned to each of the 24 possible orders of tracking on the four diamond paths. Instructions were to keep the cursor on the moving target, or as close as possible, while it steadily moved counter-clockwise twice around the diamond. Pre- and post-test pinch force maximal voluntary contraction (MVC) measures were used to scale the actual force levels tested to each participant's strength and to assess fatigue. Each participant completed 15 practice trials and 5 test trials per diamond path for a total of 80 trials. Two dependent variables, root mean squared error (RMSE) and coefficient of variation of the error (CVE), were calculated to assess accuracy and variability, respectively, for the individual digits and for combined-digit scores. Four-way repeated measures ANOVA was used to determine how accuracy and variability varied among the 4 diamond paths, the two circuits in each trial, and the four sides of each diamond. No significant differences in RMSE and CVE were found between the diamond locations, suggesting that MVC-scaled force level was not a significant factor for this task. Interestingly, the second circuit had higher RMSE and CVE than the first circuit, which may have been related to fatigue. Performance on the four sides of each diamond differed in some conditions, evidenced by a main effect of sides in CVE and significant interactions between sides and other factors for both RMSE and CVE. For accuracy, the combined-digit RMSE was significantly greater than the horizontal and vertical components generated by the two digits. For variability, all of the components were significantly different from each other. The results of this study suggest that, unlike previous results with a simple isometric pinch force tracking task, tracking performance accuracy and variability are not simply affected by MVC-scaled task force level but are differentially affected when the required coordination pattern of the two digit forces varies during the task.

Disclosures: J. Vines: None. **M. Schleicher:** None. **R. Adlis:** None. **D. Lee:** None. **C. Hilton:** None. **R.T. Eakin:** None. **L.D. Abraham:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.08/LL1

Topic: E.04. Voluntary Movements

Title: Kinematic fluctuation contributes to unintentional error in writing movements

Authors: *C. YAMADA[1], Y. ITAGUCHI[2], K. FUKUZAWA[3]
[1]Waseda Univesity, Tokyo, Japan; [2]Dept. of Syst. Design and Engin., Keio Univ., Kanagawa, Japan; [3]Waseda Univ., Shinjuku-ku, Japan

Abstract: A slip of the pen is one of the most typical action slips in our daily life. Action slip is unintentional error in action or sequence of behavior that cannot be attributed to failure of memory. It has been said that action slip occurs when people perform many simple skilled action automatically, and they do not explicitly monitor the feedback from each action. In terms of action slips in writing, previous studies reported that an experimental approach called Rapid Repeated Writing (RRW) can induce slips of the pen. RRW requires participants to write one character repeatedly as fast as possible for a few minutes. During RRW, some people mistakenly write different characters from what they intend to write.
Previous models assumed that improper activation and triggering of a schema (a motor memory unit) contribute to slips of the pen. Though several studies had suggested that improper activation caused by repetitive movement of RRW results in slips of the pen, it remains unclear what is a critical factor for improper triggering of a schema of an unintended character. We hypothesized that kinematic fluctuation in writing movements causes temporal discrepancy in the timing of the predicted and actual feedbacks and leads to improper triggering of an unintentional schema. The present study investigated how kinematic aspects of writing movements change just before slips of the pen occur.
In the experiment, 30 participants performed two-minutes RRW of one Hiragana character for five trials. We recorded their writing movements to calculate writing time per character, interval time between characters, and trajectory and velocity of the movements. These indices were compared between three periods: the initial period and the last period of a trial, and a period just before a slip occurred.
As a result, slips of the pen was observed in 14 participants. The one-way ANOVAs showed that both writing time and time interval in the pre-slip and the last periods were significantly longer than that in the initial period, and the variance of time interval in the pre-slip and the last periods were also significantly larger than that in the initial period. In contrast, the variance of writing time was significantly larger in the pre-slip period than in the initial and the last periods. In addition, kinematic fluctuations in trajectories of writing movements were observed in the pre-slip period. The larger variance of writing time and useless kinematic fluctuations in the pre-slip period suggest that temporal discrepancy in the timing of the predicted and actual feedbacks leads to improper triggering of schemas and induces slips of the pen.

Disclosures: C. Yamada: None. **Y. Itaguchi:** None. **K. Fukuzawa:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.09/LL2

Topic: E.04. Voluntary Movements

Support: NIAMS NIH award# R01 AR050520 to F.V.C
NIAMS NIH award# R01 AR052345 to F.V.C
DOD award# MR150091 to F.V.C

Title: Ipsilateral corticospinal excitability and contralateral corticomuscular drive are related phenomena

Authors: *C. M. LAINE[1], N.-H. KO[1], F. J. VALERO-CUEVAS[1,2], B. E. FISHER[1]
[1]Div. of Biokinesiology and Physical Therapy, [2]Dept. of Biomed. Engin., USC, Los Angeles, CA

Abstract: Cortical drive to contralateral muscles contains a beta-band (~20 Hz) oscillation during constant-force isometric tasks, such as a precision pinch, but subsides in more complex tasks. Several lines of evidence suggest that transitioning away from isometric force production engages dispersed networks, many of which project to bilateral motor cortices. Separately, others have shown that complex unimanual tasks also increase ipsilateral corticospinal excitability. Here we test the hypothesis that these two phenomena are related. We recorded beta-band drive to the right abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles of 10 participants as they pinched either 1) a wide spring or 2) slender spring, at matched forces (< 3N). The slender spring is prone to buckling, and thus requires more dynamic, but minute, changes in the direction of pinch force. Compression of this spring has been shown to reduce beta-band synchronization between the EMG signals recorded from the FDI and APB muscles (a measure of shared corticomuscular drive). In contrast, compressing a wide spring is known to maximize beta-band intermuscular synchronization. During spring compression of each spring, single-pulse transcranial magnetic stimulation (TMS) of the ipsilateral (right) motor cortex was used to measure ipsilateral corticospinal excitability by producing motor evoked potentials (MEPs) in the unengaged (left) FDI. Our results show that slender spring compression was associated with decreased right hand FDI-APB synchronization ($p = 0.004$, signed rank test) and increased left hand MEP amplitudes ($p = 0.014$, signed rank test), as compared with compression of the wide spring. Across participants, the average change in MEP amplitudes between the two tasks was negatively correlated with the average change in FDI-APB synchronization (Spearman's $rho = -0.82$, $p = 0.007$). This strong association suggests that the oscillatory content of cortical drive to contralateral muscles is modulated by the same processes that inhibit the excitability of the ipsilateral cortex during unimanual tasks. While further work is needed to understand the connection between motor cortex oscillations and excitability, our data do emphasize that the oscillatory drive to muscles is indicative of extensive (and bilateral) upstream network activity.

Disclosures: C.M. Laine: None. **N. Ko:** None. **F.J. Valero-Cuevas:** None. **B.E. Fisher:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.10/LL3

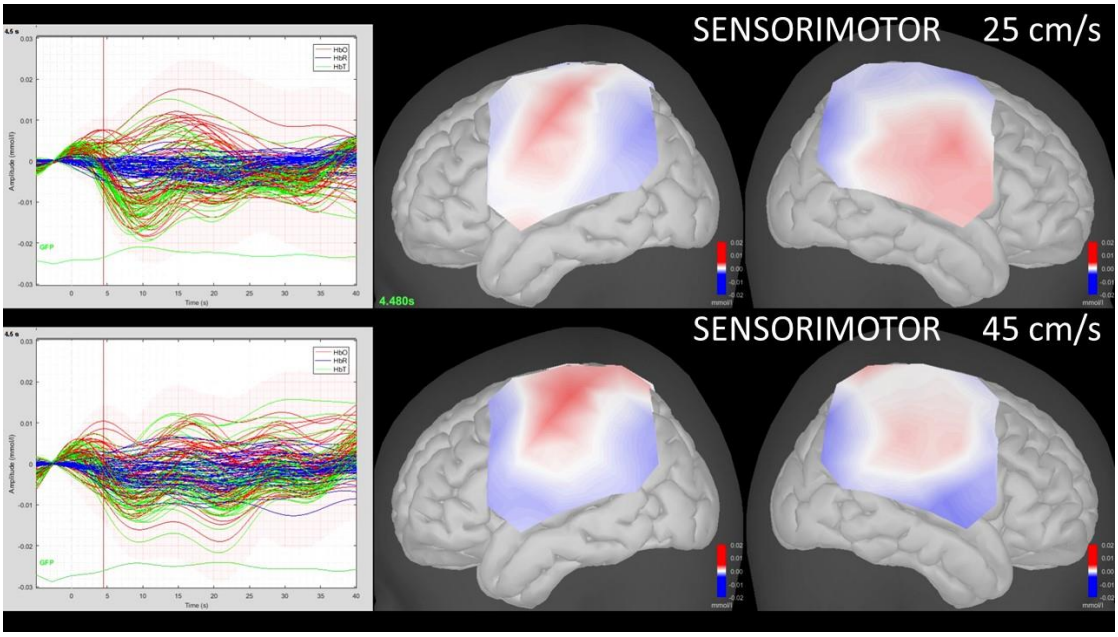
Topic: E.04. Voluntary Movements

Support: Barkley Foundation

Title: An fNIRS study of sensorimotor cortical hemodynamics in hand motor tasks coupled with pneumotactile stimulation at different traverse velocities

Authors: *M. HOZAN[1,2,3], J. GREENWOOD[1,2,3], M. K. SULLIVAN[1,3], S. M. BARLOW[1,2,3]
[1]Ctr. for Brain, Biol. and Behavior, [2]Biol. Systems Engin. Dept., [3]Dept. of Special Educ. and Communication Disorders, Univ. of Nebraska-Lincoln, Lincoln, NE

Abstract: BACKGROUND: The cerebral hemodynamic response (HR) is accessible by functional near-infrared spectroscopy (fNIRS) while participants perform repetitive motor activity and simultaneously receive patterned somatosensory stimulation. OBJECTIVE: Assess the spatiotemporal pattern of the cerebral HR in response to controlled sensorimotor pacing during precision grip in one hand performed at two distinct velocities (25 & 45 cm/sec) simultaneous with saltatory pneumotactile stimulation of the glabrous hand. The effects of specific motor and sensory velocities on the evoked HR, and the correlation between them will be assessed. 1) Activation of both pre- and post-central hand/digit representation is predicted in hemisphere contralateral to the active hand. 2) Evoked HR responses (HbO) expected to show dependence on task and stimulation velocity. METHODS: Prospective study involving 20 neurotypical adults (19-35 yrs). Saltatory pneumotactile stimulation (60 ms pulses, 8-chan array) traversed the glabrous hand (D1-D5) at 25 and 45 cm/s, while subjects performed precision grip at a matching velocity. A random-balanced block design was used for stimulus presentation (20s stim ON; 20s stim OFF; 10 reps/velocity) during fNIRS data acquisition (NIRx Scout, montage of 16 dual-tip LED emitters (760 nm, 850 nm) and 20 detectors (7.8125 Hz sampling rate) placed bilaterally over motor and somatosensory cortices. Anatomic MRI (3T; MPRAGE; 0.5x0.5x1.0 mm; TE=4.92 ms; TR=20 ms) was acquired for fNIRS co-registration using a Polhemus head digitizer. RESULTS: 1) A primary HR peak in HbO at 4.5 s on the contralateral hand pre- and post-central gyri, with a significantly larger evoked HbO signal for the 45cm/s compared to the 25cm/s condition. 2) A secondary HR peak at 13 s, including expansion of evoked HbO signal Broca's area, face M1, and supramarginal gyrus. CONCLUSION: Non-invasive fNIRS methodology reveals sensorimotor topography associated with grip dynamics and saltatory pneumocutaneous stimulation at controlled velocities. Supported in part by the Barkley Foundation (Barlow)



Disclosures: M. Hozan: None. **J. Greenwood:** None. **M.K. Sullivan:** None. **S.M. Barlow:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.11/LL4

Topic: E.04. Voluntary Movements

Title: Reconsolidation task performed with untrained limb enhances motor skill acquisition

Authors: *T. GYODA, K. ISHIDA, T. WATANABE, I. NOJIMA
Nagoya Univ., Nagoya, Japan

Abstract: Motor skills are acquired through training and rely on consolidation (stabilization of the motor memory obtained during training). Reconsolidation, in which previously consolidated memories become temporarily unstable, can further enhance the skill acquisition by re-stabilization. Also, motor skill acquisition is greater with variable than constant practice (Wymbs et al., Curr Biol, 2016). Moreover, intermanual transfer is a well-accepted phenomenon of motor learning and has important implications for rehabilitation. Here, we investigated whether a reconsolidation task performed by the hand opposite to the one originally used for practice would enhance performance gain and whether the performance gain would depend on the type of reconsolidation task (variable or constant practice). Subjects performed a sequential visual isometric pinch force task (SVIPT), which required them to move a horizontal screen cursor

between a start position and different target gates as accurate and fast as possible by producing pinch force with their right (R) or left (L) hand. In this task the skill was acquired by shifting the speed-accuracy-tradeoff function. In addition to the original SVIPT (task A), we create the modified version of the SVIPT (task B), in which the original sequence was intermixed (variable practice). The subjects were assigned into one of three groups (RA-LA-RA, RA-LB-RA, or RA-RA). In session 1, all subjects performed RA task (task A with R hand) for 4 blocks. In session 2 (6 hours after session 1), the subjects in the RA-LA-RA and RA-LB-RA groups practiced either LA or LB task 4 blocks, depending on the group assignment, after a brief reactivation RA (1 block). In session 3 (24 hours after session 1), all subjects were tested with the RA task. Based on the average movement time and error rate, we evaluated the motor skill acquisition by quantifying changes in the speed-accuracy tradeoff function (Reis et al., PNAS, 2009). We found that the motor skill acquisition in session 3 in the RA task was higher for the RA-LA-RA and RA-LB-RA groups than the RA-RA group. However, there was no significant difference between RA-LA-RA and RA-LB-RA groups. These findings suggest that a reconsolidation task performed by the unpracticed hand can enhance the acquisition of fine motor skills regardless of the reconsolidation task type (variable or constant).

Disclosures: T. Gyoda: None. **K. Ishida:** None. **T. Watanabe:** None. **I. Nojima:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.12/LL5

Topic: E.04. Voluntary Movements

Support: European Space Agency, Prodex (BELSPO, Belgian Federal Government)

Title: Multimodal reference frame during rhythmic arm movements in different body orientations with respect to gravity

Authors: *L. OPSOMER[1,2], F. CREVECOEUR[1,2], J. MCINTYRE[3,4,5], J.-L. THONNARD[1,2], P. LEFÈVRE[1,2]
[1]Inst. of Neurosci., Univ. Catholique De Louvain, Bruxelles, Belgium; [2]ICTEAM, Univ. Catholique de Louvain, Louvain-la-Neuve, Belgium; [3]CNRS, Univ. Paris Descartes, Paris, France; [4]Hlth. Division, Tecnalia Res. & Innovation, San Sebastian, Spain; [5]Ikerbasque Sci. Fndn., Bilbao, Spain

Abstract: Dexterous manipulation of objects requires predicting the inertial consequences of one's movements, but also taking into account the action of gravity on our body and the objects we interact with. One consequence is that we expect movement kinematics and dynamics to be parameterized in an allocentric (gravity-based) reference frame. The present work addressed this

aspect of motor control by studying object manipulation during rhythmic arm movements in different body orientations with respect to gravity.
Eight subjects participated in the experiment. They were instructed to perform arm oscillations with an object held in precision grip. The oscillations were performed with stretched arm in the vertical direction with respect to the body. The subjects were seated and attached to a chair that could take three positions: UPRIGHT (head up), SUPINE (face up) or UPSIDE-DOWN (feet up). They performed four blocks of 25 oscillations per position. The position and acceleration of the manipulated object as well as the forces applied by the fingers on the object were measured. Analysis of the movement kinematics revealed a strong influence of the change in position consistent with an allocentric reference frame. Indeed, the Positive Acceleration Duration of the movement (PAD, acceleration being positive when directed towards the head) was significantly influenced by the position of the chair: while significantly lower than 50% of a full cycle duration in UPRIGHT position, this asymmetry was neither observed in SUPINE nor in UPSIDE-DOWN position. However, because the asymmetry did not completely reverse in UPSIDE-DOWN position (PAD was not significantly higher than 50%), we cannot conclude that the kinematics obeyed to a strictly allocentric coding. It could be that more repetitions are necessary for a complete adaptation to this unfamiliar condition to occur. Analysis of the dynamics showed that the subjects were able to anticipate the variations in load force and to modulate their grip force adequately in the three chair positions. This was revealed by the time lag measured between the load force rate and the grip force rate, which was similar in the three positions and close to zero, and by the correlation between the two forces, which was similar or larger in UPSIDE-DOWN position in comparison with the UPRIGHT position. These results show that the CNS rapidly accounts for changes in the direction of the gravitational force during movement planning and control. However, more training might be needed for gravity to be integrated optimally in UPSIDE-DOWN position.

Disclosures: L. Opsomer: None. **F. Crevecoeur:** None. **J. McIntyre:** None. **J. Thonnard:** None. **P. Lefèvre:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.13/LL6

Topic: E.04. Voluntary Movements

Support: KAKENHI 25702033

Title: Enhancement of intermuscular coherences in human upper limb during natural manipulation task

Authors: *H. OHTSUKA[1,2], S. SUZUKI[3], S. IRIE[1], R. ARIYASU[1], T. KOMIYAMA[4], T. NAKAJIMA[1]
[1]Dept Integrative Physiol, Kyorin Unversity Sch. of Med., Tokyo, Japan; [2]Dept Rehab, Heisei Ougi Hosp, Tokyo, Japan; [3]Sch. Rehab, Hlth. Sci. Univ. of Hokkaido, Hokkaido, Japan; [4]Facul Edu, Chiba Univ., Chiba City, Japan

Abstract: During the dexterous manipulation, the central nervous system regulates the neural activities of various upper limb muscles as a presumed functional unit for the motor execution. In general, natural manipulation task in the air consists of two kinematic components; a grasping component with activation of hand muscles and a lifting component with that proximal muscles. However, little is known about the coordinated and synchronized activities of these multi-joint muscles under this task.
Intermuscular electromyogram (EMG) coherence could be used to evaluate the frequency domain of the synchronous cortical drive onto motoneuron (MN) pool between different muscles.
Therefore, we examined whether the coherences during manipulation tasks was modulated depending on the muscle combinations and different motor tasks.
Healthy volunteers participated in the experiment, who all gave written informed consent. EMGs were recorded from the right biceps brachii (BB), triceps brachii (TB), flexor digitorum sperficialis (FDS), and extensor digitorum communis (EDC) muscles. Subjects were required to maintain grasping and lifting task of cubical box (4 cm on a side, 70 g weight) with thumb, index and middle fingers (G&L task) for 30 s. Coherence spectrum were calculated from six EMG pairs (BB-TB, BB-FDS, BB-EDC, TB-EDC, TB-FDS, or FDC-EDC pair) for 4 trials (4 trials x 30 s).
As a result, peak coherence values (range of values: 15-35 Hz) in BB-TB, BB-FDS, and TB-EDC pairs during G&L task were significantly larger than that the isolated co-contraction task with the target muscle pairs. As for the coherences of BB-EDC and TB-FDS pairs, however, there were no significant differences between both tasks. These effects were also obtained from recording of intramuscular EMG using needle electrodes. Interestingly, the enhancement of coherent values was not observed when mimicking the shape of fingers and elbow angle in the air (no object) under the similar situation of EMG activities with G&L task.
Taken in sum, these results suggest that the central nervous system during execution of manipulation task regulates oscillatory synchronous drive onto MN pool depending on the combination of muscles, and the combined effect of manipulation-related afferent feedback (e.g., tactile afferents of finger tips and object load) and central commands promotes the synchrony of these pairs.

Disclosures: H. Ohtsuka: None. **S. Suzuki:** None. **S. Irie:** None. **R. Ariyasu:** None. **T. Komiyama:** None. **T. Nakajima:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.14/LL7

Topic: E.04. Voluntary Movements

Support: University of Texas Brain Pilot

Title: MEG correlates of fine motor control

Authors: *P. FERRARI[1], C. HAN[2], L. D. ABRAHAM[4], M. H. MCMANIS[5], D. M. SCHNYER[6], J. S. SULZER[3]
[2]Biomed., [3]Mechanical Engin., [1]Univ. of Texas At Austin, Austin, TX; [4]Kinesiology and Hlth. Educ., [5]Univ. of Texas at Austin, Austin, TX; [6]Univ. of Texas, Austin, Austin, TX

Abstract: Fine motor control is essential for activities of daily living, but is often the first casualty of neurological injury. Restoration of fine motor control depends on our ability to characterize it. Recent research in functional magnetic resonance imaging suggests models of fine motor control from connectivity in the sensorimotor (SM) network to distributed patterns of activation in the motor cortex. However, these models lack temporal specificity. Thus, we aimed to identify the modulation of sensory-motor networks involved in fine motor control using magnetoencephalography (MEG). Viewing fine motor control as a dynamic operation combining sensory, motor and attentional networks within a predictive based system, we hypothesize that these networks will reflect task demands and be predictive of behavioral performance. This study used a custom-designed MR/MEG compatible force sensor capable of measuring differential forefinger and thumb forces which were mapped to the position of a two-dimensional cursor. Our precision grip task required subjects to control forefinger and thumb forces (~20N) at increasing and decreasing magnitudes as they tracked a constant velocity visual target along a 45 degree edge with a 6 sec duty cycle. In an 'Uncoupled' condition, forefinger and thumb forces push the cursor horizontally and vertically, respectively, requiring fine-motor control. A 'Coupled' condition was also tested where the forces were averaged and cursor position fixed along the edge, required only force magnitude control. 10 subjects (5 females, mean age 26.0 years) performed 120 trials of each condition at force ranges dependent on their maximum voluntary contraction. In a preliminary approach, we analyzed the movement-evoked fields anticipating larger activation in the ipsilateral hemisphere for the uncoupled over the coupled task. MEG was time-locked to initial movement parameters and filtered from 0.5 - 40Hz. After artifact cleaning, cortical source estimation was performed using a minimum norm solution utilizing a BEM head model, within the MNE python toolbox. Individual anatomy and brain activity were normalized using freesurfer and the group-averaged responses represented as statistical parametric maps. The initial results reveal that within the first 50ms after movement

onset a more distributed activation pattern for the uncoupled vs the coupled task evolves, with fine-motor control involving an extensive contralateral network involving motor, sensory and visual cortices, as well as ipsilateral involvement. These findings may reflect widespread coupling between sensory and motor systems underlying the performance of fine-motor control.

Disclosures: P. Ferrari: None. **C. Han:** None. **L.D. Abraham:** None. **M.H. McManis:** None. **D.M. Schnyer:** None. **J.S. Sulzer:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.15/LL8

Topic: E.04. Voluntary Movements

Support: FWO Odysseus, Belgium

Title: Mismatch between expected and observed movements: Uncertainty alters motor resonance

Authors: *G. RENS, M. DAVARE
Dept. of Movement Sci., KU Leuven, Heverlee, Belgium

Abstract: Accurate estimation of an object's weight is an important prerequisite for predictive force scaling in the context of skilled object lifting. It has been demonstrated that humans are not only capable of extracting information about object weight from visual object properties and sensorimotor memories, but also by observing hand-object interactions performed by other individuals. In the present study, we investigated (1) how lifting actions are implemented into the observer's motor repertoire and (2) used to plan a skilful lift. Subjects first observed an actor grasping an object and then performed the same action on the same object. In order to probe motor resonance mechanisms, we applied single pulse transcranial magnetic stimulation (TMS) over the primary motor cortex (M1) and measured corticospinal excitability (CSE) while subjects observed the actor's movements. Subjects were divided into two groups. The first group *(n=18)* observed lifts of two objects with congruent properties (i.e. large-heavy and small-light objects). In the second group *(n=13)*, we added two objects with incongruent properties (i.e. large-light and small-heavy objects). In the first group of subjects observing lifts of objects with congruent properties, we found that CSE was significantly higher when subjects observed lifts of the large-heavy compared to the small-light objects (*p=0.04)*. However, in the second group of subjects observing both congruent and incongruent objects, modulation of CSE was not driven by the perceived object weight but rather by a surprise factor. That is, irrespective of weight, CSE was significantly lower when subjects observed lifts of congruent compared to incongruent objects *(p<0.01)*. Interestingly, at the behavioural level, the second group of subjects was still able to accurately extract information about weight for each of the four objects and correctly scale their

own fingertip forces. These results reveal that motor resonance can be driven by perceived movement kinematics and that introducing uncertainty between predicted and observed kinematics alters motor resonance. We therefore argue that the influence of mirror neurons on M1 is not robust, but can be biased by cortical areas processing the expectation uncertainty.

Disclosures: G. Rens: None. **M. Davare:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.16/LL9

Topic: E.04. Voluntary Movements

Support: Research was sponsored by the U.S. Army Research Office and the Defense Advanced Research Projects Agency (DARPA) was accomplished under Cooperative Agreement Number W911NF-15-2-0016.
NIH/NIGMS U54GM104942 AS

Title: Decoding muscle activation patterns from kinematics using a detailed musculoskeletal model with active muscle stiffness

Authors: *A. SOBINOV[1], M. BOOTS[1], V. GRITSENKO[1], M. MANSOURI[3], C. BERINGER[4], M. BONINGER[4], L. E. FISHER[5], J. L. COLLINGER[4], R. A. GAUNT[5], S. YAKOVENKO[2]
[2]Human Performance, [1]West Virginia Univ., Morgantown, WV; [3]Univ. of Pittsburgh, Monroeville, PA; [5]Physical Med. and Rehabil., [4]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: An intuitive myoelectric prosthesis controller would responsively follow a user's motor intent. In transradial amputees, the motor signals from residual muscles can be accessed using implantable electromyography (EMG) electrodes. Our approach to create an intuitive controller is to extract signals from spared muscles and compute intended prosthesis movement from the movement of a dynamic musculoskeletal model of an intact limb. The main obstacles responsible for discrepancies between intended and simulated movements in this biomimetic approach are the complex EMG to muscle recruitment relationship and muscle identification errors.
To compensate for these problems, we developed a transformation between the full complement of task-dependent computed muscle activations (CMA) and EMGs recorded from extrinsic hand muscles in healthy subjects and a transradial amputee. The CMAs were obtained from recorded and simulated hand kinematics (e.g., hand grasp, wrist flexion, and thumb movement in multiple wrist postures) using an inverse of the musculoskeletal system with Hill-type muscle models. The generation of CMAs is an underdetermined problem requiring joint stiffness and metabolic cost constraints to transform 18 degrees of freedom to 34 muscle activations. Task-dependent

active joint stiffness was introduced to impose the coactivation of antagonistic muscles, which is commonly present in hand movements. Using published measurements of wrist joint stiffness in similar movements (0.1 Nm), we decreased stiffness for the distal joints (CMC, MCP, PIP, DIP) in proportion to segment inertia. The solution to the inverse problem was tested by replay of CMAs for each movement in real-time forward dynamic simulations. CMAs reproduced the desired kinematics with less than 5° error for each joint. To test that the resulting CMAs can be used in a prosthesis, we did a regression with the CMAs against a dataset of surface and intramuscular EMGs from subjects performing hand movements.
Our preliminary results suggest that CMAs are closely related to recorded EMGs (normalized residuals <10%). The correlation between CMA and EMG patterns was stronger in the presence of the variable stiffness constraint than without it or with constant stiffness. The regression coefficients could identify mislabeled muscles (e.g. finger instead of wrist flexors) from synergies with distinct functions in the selected movement set. The method of computing muscle activity using joint stiffness constraints matches experimental data. The CMAs can be used for automatic calibration and lead to intuitive control of a biomimetic prosthesis.

Disclosures: A. Sobinov: None. **M. Boots:** None. **V. Gritsenko:** None. **M. Mansouri:** None. **C. Beringer:** None. **M. Boninger:** None. **L.E. Fisher:** None. **J.L. Collinger:** None. **R.A. Gaunt:** None. **S. Yakovenko:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.17/LL10

Topic: E.04. Voluntary Movements

Support: NIH NICHD P2CHD086844

Title: Characterizing motor cortex interhemispheric inhibition and relationships with manual dexterity in older adults

Authors: *M. R. BORICH[1], S. L. WOLF[2]
[1]Emory Univ., Atlanta, GA; [2]Emory Univ. Sch. Med., Atlanta, GA

Abstract: Unimanual and bimanual movements are mediated by interhemispheric inhibition (IHI) and facilitation between primary motor cortices (M1). IHI is hypothesized to be abnormal after stroke, and may contribute to persistent motor impairments. IHI can be characterized non-invasively using transcranial magnetic stimulation (TMS)3. Younger, healthy populations (age 20-40) demonstrate maximal IHI under specific TMS conditions. Despite evidence of changes in brain structure and function with aging, IHI has not been comprehensively characterized in older adults. The purpose of this study was to characterize IHI and evaluate relationships with hand

dexterity in older adults without history of neurologic conditions. Fifteen neurologically intact right handed individuals (age: 53-81, mean ± SD: 68.7 ± 6.6y, 6 female) completed a single TMS evaluation of IHI. Standard TMS hotspot and resting motor threshold (RMT) procedures were performed with the first dorsal interosseous (FDI) as the target muscle. To elicit IHI, a single suprathreshold (120% RMT) conditioning stimulus (CS) was applied over the contralateral motor cortex (M1) prior to a single suprathreshold (120% RMT) test stimulus (TS) at different interstimulus intervals (1, 5, 8, 9, 10, 11, 12, 15, 25, 50ms). Responses were normalized to unconditioned TS responses (IHI ratio: Conditioned/Unconditioned). Timed performance on the Nine Hole Peg Test (NHPT) was used to evaluate manual dexterity bilaterally. The TMS protocol was repeated with 10 individuals on a separate day to evaluate inter-session variability. Results demonstrated that in older individuals, significant IHI was present for ISIs 8-12ms and the ISI eliciting maximum IHI varied between individuals and between sessions. It was also observed that greater maximal IHI was associated with better NHPT performance bilaterally. These findings demonstrate that IHI is present in similar magnitudes and at similar ISIs compared to previous reports in young adults. However, there is substantial inter-individual and inter-session variability that makes between-individual comparisons and longitudinal assessments challenging. Results show that greater IHI is associated with better hand dexterity which may inform future studies aimed at evaluating neural markers of and developing treatments for motor dysfunction in clinical populations.

Disclosures: M.R. Borich: None. **S.L. Wolf:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.18/LL11

Topic: E.04. Voluntary Movements

Support: Fonds Wetenschappelijk Onderzoek (Belgium)

Title: Effects of TMS over the anterior intraparietal area on force and perceptual estimates in the size-weight illusion

Authors: V. VAN POLANEN[1], G. BUCKINGHAM[3], *M. DAVARE[4,2]
[1]Fac. of Kinesiology and Rehabil. Sci., KU Leuven, Heverlee, Belgium; [2]Dept. of Movement Sci., KU Leuven, Leuven, Belgium; [3]Univ. of Exeter, Exeter, United Kingdom; [4]Inst. of Neurol., London, United Kingdom

Abstract: When lifting an object, its physical properties (e.g. size) are used to appropriately scale fingertip forces, usually ensuring a smooth and efficient lift. If this motor plan is incorrect, forces are rapidly adjusted and the scaling is updated for next lifts with similar objects. However,

while force parameters are precisely fine-tuned, perception of object weight can still be biased. For instance, in the size-weight illusion, a smaller object is consistently reported as feeling heavier than a large object of equal mass. The neural mechanisms underlying the control of either motor or perceptual parameters remain unclear. We hypothesised that the anterior intraparietal area (AIP), known for encoding visual object properties and for planning fingertip forces during lifting, could play a role in the size-weight illusion. To address this issue, we applied continuous theta burst stimulation (cTBS) over AIP in three different subject groups before they lifted size-weight illusion inducing objects. Individuals received cTBS (80% of active motor threshold) on either AIP, the primary motor cortex (M1) or took part in a control condition in which cTBS was applied over AIP with a weak, inefficient, intensity (40% of active motor threshold). After stimulation, subjects were asked to lift small light, small heavy, large light, or large heavy objects in a randomized order, and to verbally report the object's weight. These four objects allowed us to compare force scaling and weight perception between different object sizes and weights. We found no effects of cTBS on the perception of object weight. In all conditions, subjects reported a size-weight illusion and were able to distinguish between light and heavy objects. However, we found that force scaling was affected by cTBS. The loading phase duration was not scaled to size following cTBS over either AIP or M1 (size × cTBS interaction), where these effects seemed larger in the AIP cTBS group. In the very first trials, where the object weight was still unknown, grip force scaling to object size was reduced following cTBS over AIP (size × cTBS interaction). These results suggest that AIP is involved in force scaling to object size, without playing a role in object perceptual properties. This specific effect on motor parameters is in line with previous research reporting independent effects on force scaling and weight perception in size-weight illusion objects.

Disclosures: V. Van Polanen: None. **G. Buckingham:** None. **M. Davare:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.19/LL12

Topic: E.04. Voluntary Movements

Title: Motor unit coherence indicates changes in corticospinal influence during different hand motor tasks

Authors: C. KIM[1], M. A. PEREZ[2], *L. M. MCPHERSON[1]
[1]Florida Intl. Univ., Miami, FL; [2]Dept. of Neurolog. Surgery, The Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL

Abstract: There is increasing evidence that both corticospinal and reticulospinal motor pathways contribute to the control of hand muscles in humans and that the relative extent of this

contribution may differ during tasks that require precise vs. gross control. For example, recent findings using transcranial magnetic stimulation over the hand representation of the primary motor cortex showed that corticospinal excitability and intracortical inhibition decreased to a larger extent during power grip (gross motor control) than during index finger abduction and precision grip (fine motor control; Tazoe and Perez, 2017). Here, we aim to characterize the neural drive across these hand motor tasks using motor unit coherence analysis.We asked uninjured subjects (n = 6) to perform index finger abduction, precision grip, and power grip while maintaining 10% of maximal voluntary contraction with the right first dorsal interosseous (FDI) muscle. High-density surface electromyography (EMG) was obtained from a 64-channel grid placed on the FDI, and real-time visual feedback of rectified, smoothed EMG from a central channel of the grid was provided during each trial. High-density EMG was decomposed into motor unit spike trains using an established algorithm (Negro et al., 2016). Composite spike trains containing the discharge of multiple simultaneously firing motor units were used to calculate motor unit coherence, which was compared among the three tasks by summing the coherence within four different frequency bins: common drive (1 - 2 Hz), alpha (5 - 12 Hz), beta (15 - 30 Hz), and gamma (30 - 60 Hz).We found that motor unit coherence in the beta and gamma bands decreased by ~50% during power grip compared with index abduction and precision grip. Because coherence in these higher frequency bands is thought to reflect motor cortical/corticospinal influences, our preliminary findings suggest a decreased contribution from these structures during gross compared with fine hand motor tasks, consistent with previous results (Tazoe and Perez, 2017).

Disclosures: C. Kim: None. **M.A. Perez:** None. **L.M. McPherson:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.20/LL13

Topic: E.04. Voluntary Movements

Support: NIH grant R01 NS082865 05

Title: High-dimensional control of volitional hand movements

Authors: Y. YAN, D. D. MOORE, J. M. GOODMAN, *B. P. DELHAYE, S. J. BENSMAIA
Dept. of Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: The hand - an extraordinarily sophisticated and versatile organ - is our primary means for interacting with objects. Despite its staggering complexity, hand control is precise and effortless. A compelling hypothesis for how the brain manages to achieve this level of dexterity is that it restricts its control of the hand to a smaller, more manageable subspace than the full

range of movements of which the hand is capable. This subspace can be broken down into sets of coordinated movement primitives termed synergies. However, the vast majority of studies on putative synergies have examined the kinematics within a single task paradigm, which may lead to underestimation of the dimensionality of hand movements. Moreover, the total number of synergies is generally inferred from the explained variance in the kinematics, which may discard some meaningful (volitionally controlled) components of these movements. To address these potential limitations, we measure - using a camera-based motion tracking system - hand kinematics as human participants perform several manual tasks, namely grasping, typing, fingertip-to-fingertip touching, and American Sign Language finger spelling. We then analyze the measured kinematics with principal component analysis (PCA), as has been previously done, and explore the generalizability of high-variance principal components across tasks. We also implement machine learning techniques to assess the degree to which the dimensionality of hand kinematics can be reduced without losing any precision in hand shaping prior to contact. First, we find that hand synergies inferred using the standard approach fail to generalize across paradigms. Second, lower-variance principal components are important for correctly conforming the hand to task demands, suggesting that they are under volitional control rather than reflecting experimental or motor noise. We conclude that volitional hand movements occupy a higher-dimensional space than previously suggested.

Disclosures: Y. Yan: None. **D.D. Moore:** None. **J.M. Goodman:** None. **B.P. Delhaye:** None. **S.J. Bensmaia:** None.

Poster

671. Voluntary Movements: Finger and Grasp Control: Normal Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 671.21/LL14

Topic: E.04. Voluntary Movements

Support: NIH R01 NS 082865

Title: The perception of the angle of a finger joint is independent of load

Authors: *B. PRENDERGAST, J. M. GOODMAN, M. BOYARINOVA, J. E. WINBERRY, S. J. BENSMAIA
Dept. of Organismal Biol. & Anat., Univ. of Chicago, Chicago, IL

Abstract: Hand proprioception plays a key role in our ability to dexterously interact with objects. Little is known, however, about how precisely and accurately we sense hand kinematics and kinetics. We attempt to fill this gap with a series of psychophysical experiments to determine the acuity of human hand proprioception and to assess the extent to which kinematic and kinetic components of proprioception might interact with one another. First, we assessed how resistive

force impacts subjects' ability to perceive index finger position. Second, we investigated whether changes in joint angle might modulate the perception of loads applied to the finger. We found that varying the load acting on the finger did not affect subjects' perceived joint angle when the posture was produced actively. In contrast, load did affect the perceived finger angle when it was imposed by the experimenter. Furthermore, changes in joint angle did not affect subjects' perception of loads applied to the finger; we verified that the stability of load perception across postures was not mediated by cutaneous signals. We conclude that the perception of hand posture is robust across torques imposed on the fingers despite (presumed) changes in the peripheral sensory input and that the perception of load is independent of joint angle.

Disclosures: B. Prendergast: None. **J.M. Goodman:** None. **M. Boyarinova:** None. **J.E. Winberry:** None. **S.J. Bensmaia:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.01/MM1

Topic: E.05. Brain-Machine Interface

Support: Army Research Office (ARO) Grant W911NF-16-1-0368. This is part of the collaboration between US DOD, UK MOD and UK Engineering and Physical Research Council (EPSRC) under the Multidisciplinary University Research Initiative (MURI).
NIH Grant 1R01NS104923-01

Title: Modeling functional dependencies in high-dimensional spike-field activity

Authors: *R. BIGHAMIAN[1], Y. WONG[3], B. PESARAN[4], M. M. SHANECHI[2]
[2]Electrical Engin., [1]USC, Los Angeles, CA; [3]Physiology, and Electrical and Computer Systems Engin., Monash Univ., Clayton, Australia; [4]New York Univ. Ctr. for Neural Sci., New York, NY

Abstract: Behavior is simultaneously encoded across multiple spatiotemporal scales of brain activity, from neuronal spikes to local field potentials (LFP). Estimating the functional dependencies between spikes and fields during behavior can help build more accurate neural encoding models and decoders. However, learning these dependencies in high-dimensional recordings is challenging because of the large number of spike-field pairs, which makes standard learning techniques prone to overfitting. Thus functional spike-field dependencies are often explored only between one or few electrode pairs rather than simultaneously across a large network. Here we present a sparse model-based approach for estimation of functional dependence in high-dimensional spike-field networks during behavior, and incorporate these dependence terms in neural encoding models. We model the spiking activity of each neuron as a

point process whose firing rate is modulated not only by behavior, but also by the field features across the entire recorded network. We then develop a learning technique that enforces sparsity in the number of spike-field network dependencies to train parsimonious encoding models. We assess the learned encoding model within cross-validation by computing the accuracy of spike prediction in the network. We validate the method using both numerical simulations and experimental data recorded from non-human primates. We find that by enforcing sparsity, our method detects the spike-field dependencies more accurately. Furthermore, compared to the model with no dependencies, our method significantly improves the spike prediction accuracy. Finally, by enforcing sparsity, the number of detected dependencies become significantly smaller without incurring any loss in prediction performance. This sparse model-based estimation technique could help learn more accurate encoding models and decoders, and investigate brain connectivity patterns across spatiotemporal scales.

Disclosures: R. Bighamian: None. **Y. Wong:** None. **B. Pesaran:** None. **M.M. Shanechi:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.02/MM2

Topic: E.05. Brain-Machine Interface

Title: Learning dynamic neural encoding models with behaviorally-relevant latent states

Authors: *O. G. SANI, M. M. SHANECHI
Electrical Engin., USC, Los Angeles, CA

Abstract: Learning a neural encoding model that describes the representation of a desired behavioral state (e.g., movement kinematics) in neural signals is critical in decoding of behavior in brain-machine interfaces (BMIs) and in studying its underlying neural mechanisms. Recent evidence suggests the existence of latent dynamics in the brain that underlie behavior. Linear state-space models (LSSM) provide a general formulation for linear neural encoding models with latent dynamics and have been successfully employed in BMI decoders. An important problem to address is the method by which behaviorally-relevant dynamics can be learned using an LSSM with a latent state. One approach is to use an unsupervised learning method such as expectation-maximization to learn an LSSM, followed by a separate supervised learning step to relate the latent states of the LSSM to behavior. However, due to the unsupervised nature of the LSSM learning step, this approach may not be efficient in terms of the dimension of the latent state (i.e., model complexity) required for describing and decoding the behavior. Here, we introduce a novel learning algorithm that can combine the flexibility of dynamic neural encoding models with latent states with the benefits of supervised learning of a desired behavior. Our algorithm aims to uncover a low dimensional latent state that is most behaviorally-relevant. For a specified

dimension, our algorithm learns an LSSM with a latent state of the specified dimension that is more accurate in describing the behavior compared with other possible states of the same dimension that are learned using unsupervised methods. This new learning algorithm can help uncover low-dimensional neural representations of a desired behavior. The learned low-dimensional encoding models also lead to efficient decoders of behavior for BMIs.

Disclosures: O.G. Sani: None. **M.M. Shanechi:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.03/MM3

Topic: E.05. Brain-Machine Interface

Support: Army Research Office (ARO) under contract W911NF-16-1-0368. This is part of the collaboration between US DOD, UK MOD and UK Engineering and Physical Research Council (EPSRC) under the Multidisciplinary University Research Initiative (MURI)
NSF under CAREER Award CCF-1453868

Title: Learning causal graphs in spike-field multiscale network encoding models

Authors: *C. WANG, M. M. SHANECHI
Electrical Engin., USC, Los Angeles, CA

Abstract: Simultaneous recordings of spikes and fields could enable analyses of causal functional connectivity patterns in the brain at multiple spatiotemporal scales and lead to accurate encoding models and decoders for brain-machine interfaces (BMIs). However, analyses of functional connectivity also necessitate deriving novel algorithms to assess causality between binary-valued spikes and continuous-valued fields, which have fundamentally different statistical characteristics and time-scales. Thus, standard measures of causality cannot be directly applied in multiscale spike-field networks.We design a novel algorithm to assess causality for multiscale spike-field activities by computing directed information, which is an information theoretic measure of causality. Directed information is difficult to estimate for general probabilistic models. Thus we develop an algorithm to estimate the directed information using two parametric models. First, we build point process generalized linear models (GLM) for each neuron's spike train to estimate its firing rate using the history of both spikes and fields and compute the directed information to a spike node from any node in the network. Second, we build linear Gaussian models for fields using the history of the estimated firing rates and the history of fields, and then compute the directed information to each field node from any node in the network. We use maximum likelihood to fit the model parameters. We then construct statistical tests to

evaluate the significance of the estimated directed information to assess causality in the network. Using simulated data from networks of various sizes, we show that our algorithm can asymptotically identify the true causality. This method could help uncover causal connectivity patterns in the brain at multiple spatiotemporal scales, and also enable accurate encoding models and decoders for BMIs.

Disclosures: C. Wang: None. **M.M. Shanechi:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.04/MM4

Topic: E.05. Brain-Machine Interface

Support: Army Research Office (ARO) under contract W911NF-16-1-0368. This is part of the collaboration between US DOD, UK MOD and UK Engineering and Physical Research Council (EPSRC) under the Multidisciplinary University Research Initiative (MURI).
NSF under CAREER Award CCF-1453868

Title: Identifying multiscale hidden dynamics to decode movement

Authors: *H. ABBASPOURAZAD[1], Y. WONG[2], B. PESARAN[3], M. M. SHANECHI[1]
[1]Electrical Engin., USC, Los Angeles, CA; [2]Physiology, Electrical and Computer Systems Engin., Monash Univ., VIC, Australia; [3]New York Univ. Ctr. for Neural Sci., New York, NY

Abstract: Dynamical modeling of neural activity can help investigate the encoding of behavior and has been an emerging direction in neuroscience. Indeed, recent work has suggested the existence of hidden neural dynamics during motor behavior. This evidence motivates developing dynamical encoding models with hidden states that represent behavior. Such models may also benefit future brain-machine interface (BMI) decoding systems. To date, dynamical encoding models have vastly characterized a single scale of activity, e.g., spikes. However, behavior is encoded across multiple spatiotemporal scales of activity, from spikes of individual neurons to larger network activity measured using local field potentials (LFPs) and electrocorticogram (ECoG). Learning a dynamical model from hybrid spike-field activity is challenging because of fundamental differences in statistical characteristics and time-scales of these signals. Spikes are binary-valued with a millisecond time-scale while fields are continuous-valued with slower time-scales. Here we present a method to learn a multiscale dynamical state-space model that identifies a hidden neural state to characterize spike-field activity simultaneously. We developed an unsupervised multiscale Expectation-Maximization (EM) algorithm that can learn the multiscale model parameters in the presence of hidden states. We validated the algorithm using

motor cortical spike-LFP data recorded from a non-human primate (NHP) performing a reach task. We used the EM to learn the multiscale state-space model and then derived the corresponding multiscale decoder to estimate the hidden states from spike-field activity. Finally, we explored whether a projection of these hidden multiscale states could decode the 7 joint angular trajectories of the arm. We found that the multiscale EM identified hidden states that could decode movement. Moreover, adding LFPs to spikes and vice versa improved decoding performance, suggesting that the hidden state was conveying non-redundant information about both spike and field dynamics. This multiscale learning algorithm can be used to study the encoding of behavior across spatiotemporal scales and has important implications for future motor BMIs.

Disclosures: H. Abbaspourazad: None. **Y. Wong:** None. **B. Pesaran:** None. **M.M. Shanechi:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.05/MM5

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, A2295R, B6453R, P1155R)
NINDS (UH2NS095548)
NIDCD (R01DC014034)
NINDS (U01NS098968)
MGH-Deane Institute
The Executive Committee on Research (ECOR) of Massachusetts General Hospital
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Title: Approaching a 24/7 at-home Braingate BCI system through design thinking, user-centered design and agile development

Authors: *J. R. BREA[1,2], B. E. SHANAHAN[1,2], J. SAAB[1,3,2], T. HOSMAN[1,2], J. D. SIMERAL[3,1,4,2], L. R. HOCHBERG[3,1,4,5,2]
[1]Sch. of Engin., [2]Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [3]VA Med. Ctr., VA RR&D Ctr. for Neurorestoration and Neurotechnology, Providence, RI; [4]Neurol., Massachusetts Gen. Hosp., Boston, MA; [5]Neurol., Harvard Med. Sch., Boston, MA

Abstract: The BrainGate intracortical BCI has been used by clinical trial participants with tetraplegia to perform daily activities including rapid typing and email, controlling devices (TV, lights) and using a robotic limb to eat or drink. Having recently demonstrated in-home 24-hour intracortical wireless recording, we are working to transform this research platform into a BCI for operating off-the-shelf devices that would be usable 24/7 by a participant and caregiver with little to no technical support. Long-term, we envision a BrainGate platform that would provide user benefit and facilitate intracortical research with remote management. To meet the right user and caregiver needs, we have taken a user-centered design (UCD) approach. UCD is a process for developing products from an end-user perspective used in industries from consumer electronics to healthcare to ensure a quality user experience. Kubler et al. (2014) first introduced the BCI field to UCD methods with usability testing EEG BCIs. Here we introduce two additional methods for transforming a predominantly Matlab-based research platform into a modern user-friendly system. First, we use a framework within UCD called Design Thinking originally developed at Stanford d.School and refined by design consulting firm, IDEO. This process involves iterative, overlapping activities: empathizing with the end user, defining the problem, ideating on solutions, prototyping, testing. By leveraging our unique experience in participants' homes 2-3 days / week and engaging key stakeholders (participant-facing team members, caregivers) and members of the broader ALS community, we create scenarios using realistic personas to guide us toward the most important end-user needs and solution design. As key system features are identified and prioritized, we use a software development methodology called "Agile" to structure our efforts into collaborative team "sprints" by which 3-5 individuals rapidly prototype and test potential solutions with stakeholders in an iterative, incremental fashion. For example, sprints to date have refined the user interface to reflect distinctions between caregiver and technician needs; enabled a single-action participant self-calibration tool; and implemented a paradigm shift to websocket methods for data flow. Leveraging Design Thinking and Agile frameworks, we continue progress toward an innovative and intuitive intracortical BCI that supports both in-home research and continuous in-home use by individuals with tetraplegia and their caregivers.

Disclosures: J.R. Brea: None. **B.E. Shanahan:** None. **J. Saab:** None. **T. Hosman:** None. **J.D. Simeral:** None. **L.R. Hochberg:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.06/MM6

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, A2295R, B6453R, P1155R)

NINDS (UH2NS095548)
NIDCD (R01DC009899)
MGH-Deane Institute
The Executive Committee on Research (ECOR) of Massachusetts General Hospital
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CAUTION: Investigational Device. Limited by Federal Law to Investigational Use.

Title: Closed-loop BCI simulation through replay of recorded neural signals

Authors: *J. N. KELEMEN[1], D. MILSTEIN[2,3], L. R. HOCHBERG[6,4,1,7,3], D. M. BRANDMAN[5,3], J. D. SIMERAL[6,4,1,3]
[1]Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [2]Dept. of Comp. Sci., [3]Carney Inst. for Brain Sci., [4]Sch. of Engin., [5]Dept. of Neurosci., Brown Univ., Providence, RI; [6]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VA Med. Ctr., Providence, RI; [7]Dept. of Neurol., Harvard Med. Sch., Boston, MA

Abstract: Intracortical brain-computer interfaces (iBCIs) provide individuals with tetraplegia a means to communicate and otherwise interact with their environment. Some iBCIs achieve this by decoding neuronal firing patterns and local field potentials to infer the user's intention to move a computer cursor and click. Because the quality of iBCI control is contingent upon the decoding algorithm and its chosen parameter values, decoder testing and parameter optimization are essential components of iBCI development. However, the number of possible combinations of parameter values can be large compared to the available testing time with iBCI study participants. Fortunately, optimal values for decoder parameters can be estimated through closed-loop simulation given sufficiently accurate simulated neural activity that can be decoded into cursor kinematics and click. Here we introduce a simulator that uses real human intracortical data recorded from implanted microelectrode arrays rather than synthetic neural activity. The data consists of spike threshold rates and local field potential power (20 ms bins) originally computed from 30kS/s signals from each electrode while participants used an iBCI to command directional cursor movements and make on-screen item selections by clicking or dwelling on the item. In order to render simulated neural activity corresponding to an instantaneous “intended” cursor movement in a particular direction, the simulator determines current direction to target and then draws samples (96 electrodes, 20 ms bins, 120 ms snippet) from instances of neural data when the participant had been commanding cursor movements in a similar direction. To render neural activity for a click, the simulator samples from snippets of data recorded when the participant was commanding a click. Using 6 distinct data sets from 3 participants, we show that cursor trajectories produced by decoding these re-sampled neural signals are comparable, according to angular error distributions, to those from real closed-loop iBCI use by trial participants. We demonstrate how, unlike in real-time testing with participants, decoders can be efficiently tested in simulation under a large number of parameter values, providing powerful initial evaluation of novel decoder parameter choices and performance. These results suggest that

this new method of simulating iBCI control by sampling from real neural data can be an efficient and effective way to investigate, test optimize, and compare decoders.

Disclosures: J.N. Kelemen: None. **D. Milstein:** None. **L.R. Hochberg:** None. **D.M. Brandman:** None. **J.D. Simeral:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.07/MM7

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, A2295R, B6453R, P1155R)
NINDS (UH2NS095548)
NINDS (U01NS098968)
The Executive Committee on Research (ECOR) of Massachusetts General Hospital
MGH-Deane Institute
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Title: Comparison of decoding accuracy: Retrospectively trained recurrent neural network and Kalman vs the same-day Kalman decoder

Authors: *T. HOSMAN[1,2], M. VILELA[1,2], J. SAAB[1,2], C. D. HEELAN[1,4], D. BRANDMAN[3,2], J. D. SIMERAL[5,1,6,2], L. R. HOCHBERG[6,2,7,1,5]
[1]Sch. of Engin., [2]Carney Inst. for Brain Sci., [3]Dept. of Neurosci., Brown Univ., Providence, RI; [4]Connexon Systems, Providence, RI; [5]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VA Med. Ctr., Providence, RI; [6]Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [7]Dept. of Neurol., Harvard Med. Sch., Boston, MA

Abstract: Intracortical brain computer interfaces (iBCIs) can enable individuals with paralysis to control a computer cursor via intended movement. Linear decoders that map motor activity to 2D cursor velocity have provided rapid on-screen typing for individuals using the BrainGate iBCI. However, linear decoders commonly degrade in performance over time, reflecting their sensitivity to nonstationarities in the neural signals. Recurrent neural networks (RNNs) can model complex nonlinear time series and are promising candidates for inferring cursor kinematics from neural signals. Sussilo et al. (2016) showed in two non-human primates that an RNN trained on days or months of previously recorded data provided equivalent or better online

control than Kalman filter trained on same-day neural data. Further, the RNN was more robust to neuron drop-out, suggesting a putative stability advantage. Although offline RNN training can be computationally demanding, Sussilo et al., demonstrated the feasibility of online RNN iBCI in NHPs, and more recent work (Heelan et al., EMBC 2018) demonstrated that an RNN with 10K inputs could run at sub millisecond update speeds. Here, we evaluated how well an RNN could decode human motor cortical signals in 2D target acquisition cursor tasks.
Data were analyzed from two participants in the BrainGate pilot clinical trial diagnosed with ALS (T7, T9). Both had two 96 channel Blackrock microelectrode arrays implanted in the hand region of dominant motor cortex. In offline analyses, an RNN and a Kalman filter were trained on 10 days of historical data (r-RNN and r-Kalman, r indicating "retrospective"). We compared the decoded kinematics from each decoder on a test data set, drawn from the subsequent research session. We also evaluated their kinematic outputs relative to the Kalman filter originally used online by the participant during that test session (termed "same-day Kalman" as it was calibrated from only within-day neural data). Decoders were evaluated using the angle error between the decoded cursor direction and the direct cursor-to-target path for every 20 ms decode step across each day tested (Mann-Whitney U test, $p<0.05$).
Across 36 (69) test days for T7 (T9), the r-RNN decoded significantly better than the r-Kalman on 84% (86%) of the days and significantly better than the same-day Kalman 53% (63%) of the test days. Overall, the retrospective RNN yielded less angle error than the r-Kalman decoder when trained on the same historical data and had similar or better performance than the same-day Kalman. These results motivate further investigation of RNNs for decoding in iBCI applications for people with paralysis.

Disclosures: T. Hosman: None. **M. Vilela:** None. **J. Saab:** None. **C.D. Heelan:** None. **D. Brandman:** None. **J.D. Simeral:** None. **L.R. Hochberg:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.08/MM8

Topic: E.05. Brain-Machine Interface

Support: DARPA NESD (N66001-17-C-4013)
Dept. of Veterans Affairs (P1155R, N9288C, B6453R, A2295R)
DARPA REPAIR (N66001-10-C-2010)
NIH BRP (5R01EB007401)
Conquer Paralysis Now (004698)
Executive Committee on Research (ECOR) of Massachusetts General Hospital
MGH-Deane Institute

Title: Processing thousands of full-broadband neural channels in real-time on a mobile platform

Authors: *C. D. HEELAN[1,3], B. E. SHANAHAN[1], L. R. HOCHBERG[4,1,5,6,2], A. V. NURMIKKO[1,2], J. D. SIMERAL[4,1,5,2]
[1]Sch. of Engin., [2]Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [3]Connexon Systems, Providence, RI; [4]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VA Med. Ctr., Providence, RI; [5]Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [6]Dept. of Neurol., Harvard Med. Sch., Boston, MA

Abstract: We present a novel FPGA circuit ("BGPipeline") capable of processing thousands of full-broadband neural channels in real-time on the mobile NeuroCoder neural processing platform. Current intracortical brain-computer interfaces (iBCIs) for human use can process and decode several hundred channels of microelectrode voltages sampled at 30kS/s. However, these desktop computer-based systems are immobile and cannot scale to the needs of high channel-count next-generation systems. We recently demonstrated wireless recording of 192 channels of wireless broadband simulated neural signals using the mobile battery-powered NeuroCoder signal processing platform (Heelan et al., 2017). Here, we extend this work with the BGPipeline FPGA circuit that implements the entire BrainGate neural preprocessing and feature extraction chain for iBCI decoding applications (Jarosiewicz et al., 2015).
We used Xilinx Vivado High-Level Synthesis (VHLS) to design the BGPipeline FPGA circuit. In that circuit, a common-average reference (CAR) circuit denoises the data by calculating the mean across a subselection of channels and subtracting this mean from each channel. A linear phase systolic FIR filter (0.3 Hz to 5.0 kHz) then bandpass filters the signals. Neural features are subsequently extracted as thresholded action potential counts ("spike rates") and frequency-band powers ("spike powers") that are summed over non-overlapping 20 ms time bins.
Two tests were used to validate the functionality of the BGPipeline circuit. First, we generated neural feature outputs using a Python reference implementation of BGPipeline given a known input test vector (sum of sinusoids). We then passed the same input test vector into a BGPipeline VHLS simulation that successfully verified the VHLS outputs against the Python outputs. Second, we examined whether BGPipeline could extract features from raw 30 kS/s multichannel data recorded from a Blackrock Digital Neural Signal Simulator (NSS). We passed signals captured from the NSS into the BGPipeline VHLS simulation and obtained outputs that exhibited the expected patterns of spiking activity and spike power.
On the current NeuroCoder hardware, BGPipeline successfully scales to 6,528 full-broadband neural channels. FPGA synthesis and implementation (placement and routing) estimate a Zynq power utilization of 2.16 watts giving this fully-mobile implementation a performance metric of ~3,022 processed channels per watt. This translation of multichannel iBCI signal processing into FPGA logic running on the mobile NeuroCoder platform in real-time is a critical step toward practical next-generation iBCIs.

Disclosures: C.D. Heelan: None. **B.E. Shanahan:** None. **L.R. Hochberg:** None. **A.V. Nurmikko:** None. **J.D. Simeral:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.09/MM9

Topic: E.05. Brain-Machine Interface

Support: Paul Allen Family Foundation
Washington Research Foundation
CSNE

Title: Implantable wireless brain computer interface

Authors: *J. NAKAHARA[1], V. RANGANATHAN[2], J. SMITH[2], C. T. MORITZ[3]
[1]Computer Sci. & Engin., The Univ. Of Washington, Seattle, WA; [2]The Univ. of Washington, Seattle, WA; [3]Rehabil. Med., Univ. of Washington, Seattle, WA

Abstract: Nearly 17,000 people are left paralyzed from Spinal Cord Injury (SCI) every year, according to the NSCISC. Along with epilepsy, these neural disorders lead to a very limited and constrained lifespan for the patients. The aim of this work is to develop a Brain-Computer Interface that leverages point-of-care neural recording and subsequent neural stimulation to treat or rehabilitate these patients for better living conditions. The current generation of devices has state-of-the art solutions for neural signal acquisition and stimulation. However, combining the two to use the recorded signal for triggering accurate, autonomous stimulation has proved to be extremely challenging. This is primarily due to the phenomenon of neural plasticity, where the evolving neural connections lead to change in signals and signal path, and the inability of existing devices to autonomously detect this change and adapt to it. Another major concern that surfaced with long term use of implanted devices is the requirement of power and communication cables that exit the skin surface from the implant and pose a risk of infection. In the best cases, implants that use batteries also have limited lifetime and have to be surgically removed to replace them. Apart from lifetime, large volume, and cost overhead of adding batteries makes them a challenge when used with implants. To address these two issues, our contribution lies in implementing a device that will enable closed-loop stimulation while incorporating wireless communication and power transfer to increase the implant's operational lifetime. Using FPGA based reconfigurable computation platform enables implementation of energy-aware reconfigurable processing for spike/LFP data. Specifically, 1) the device harvests energy from a 13.56MHz source and stores it in a supercapacitor to meet the power budget of recording, communication, computation, and stimulation. 2) It is capable of low-power wireless communication - radio frequency (RF) backscatter at 915MHz, to establish high data-rate communication between the implant and external world.
These key features eliminate any data and power cables and make the device fully implantable.

Disclosures: **J. Nakahara:** 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.; Paul Allen Family Foundation. **V. Ranganathan:** 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.; Washington Research Foundation. **J. Smith:** None. **C.T. Moritz:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.10/MM10

Topic: E.05. Brain-Machine Interface

Support: NIH/NINDS Grant R01NS086100
VA Grant I01RX001296
NIH/NINDS Grant R01NS058871
VA Grant B4195
Cleveland Clinic support.

Title: A 'Divide-and-Conquer' strategy to avoid overfitting when decoding brain state from field potentials for closed-loop control applications

Authors: *D. M. TAYLOR[1,2,3], T. JOHNSON[1,2,3], V. GOPALAKRISH[1], E. TUNC[1], S. MORALLE[1], S. RUSS[1]
[1]Neurosciences, Cleveland Clin., Cleveland, OH; [2]Cleveland VAMC, Cleveland, OH; [3]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: Brain state information from field potential data is often used in closed-loop neuromodulation and neuroprosthetic applications, and used for basic science studies. However, overfitting can become a problem when using power features from field potentials, because each recorded signal can be expanded into hundreds of individual power features. The number of power features can increase even further by extracting power from different linear combinations of the raw signals or when using features based on interactions between frequency bands. All of these permutations result in a nearly infinite number of features available from just a handful of electrodes. Such a large number of features can lead to "overfitting" when building decoding functions to predict brain state from a limited amount of data. Typically, this problem is addressed by either discarding some of the power features or averaging groups of individual features together, such as averaging the output of an FFT function into alpha, beta, & gamma bands, or averaging a phase-amplitude coupling metric over an arbitrarily-determined pair of frequency ranges. While effective, these feature reduction methods are likely discarding useful

information and/or including unnecessary noise. Therefore, we have explored what we call a 'divide & conquer' strategy for extracting more task-specific information from high-dimensional field potential power features without overfitting. The most successful divide & conquer option used a two-step process where common spatial pattern analysis was performed first to compress the useful information into a smaller number of raw signal before calculating power. In the second step, various statistical methods optimally weighted and combined different groups of the full FFT power feature set to further compress information into a smaller number of more-useful features for decoding. We applied these methods to EEG, stereo-EEG, ECoG, and LFP data collected from humans and animals to predict intended movements or predict Parkinsonian symptom state. Although optimal methods for subdividing the data varied by data type and application, significant improvement in brain state prediction could be achieved using these methods. For example, cross-validated limb movement prediction accuracy from EEGs could be improved by 25% using common spatial pattern analysis to reduce the number of signal followed by either A) building one feature per FFT frequency bin weighted across all channels or B) building one feature per channel weighted across all FFT frequency bins and then doing further feature elimination before final decoding.

Disclosures: D.M. Taylor: None. **T. Johnson:** None. **V. Gopalakrish:** None. **E. Tunc:** None. **S. Moralle:** None. **S. Russ:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.11/MM11

Topic: E.05. Brain-Machine Interface

Title: EEG-based brain-computer interface using deep neural network for point by point decoding: A pilot study

Authors: *Y. FUJIWARA[1], S. HONDA[2], J. USHIBA[3,4]
[1]Grad. Sch. of Sci. and Tech., Keio Univ., Yokohama, Japan; [2]SDM Res. Institute, Keio Univ., Kanagawa, Japan; [3]Dept. of Biosci. and Informatics, Fac. of Sci. and Technology, Keio Univ., Kanagawa, Japan; [4]Keio Inst. of Pure and Applied Sci. (KiPAS), Kanagawa, Japan

Abstract: Recently, decoding technology of Brain-Computer Interface (BCI) has been rapidly evolving. It is possible to decode Electromyogram (EMG) from Local Field Potential (LFP) (Agamemnon Krasoulis, et al.,2014) and heard speech from Electrocorticogram (ECoG) (Brian N. Pasley, et al.,2012). On the other hand, BCI decoding from Electroencephalogram (EEG) can classify the states whether participant is resting or moving right hand or left hand or legs, although the decoding time resolution remains low compared with LFP and ECoG. Generally, since, on EEG-based BCI, a waveform segmented into time windows converts into a frequency

domain features using fast Fourier transform (FFT) or the like, the refresh rate (decoding time resolution) of classification can not be raised unless time windows are overlapped. Moreover, unless we can solve the theoretical time delay problem due to the window function like the Hanning window, we can not classify on real-time no matter how much the performance of the computer improves. Even if the features are calculated in the frequency domain divided with the time window, it is difficult to distinguish by the features in the high frequency region, and there is a circumstance that it is necessary to use the feature in the low frequency region. Due to these circumstances, it is difficult to decode a dynamically changing state (EMG or speech) even when trying to update the refresh rate by overlap. Therefore, in this research, we made it possible to predict in the same refresh rate as the sampling frequency, and to solve the time lag problem by the window function. In this development, by sequentially inputting point by point data to the deep neural network including Long short-term memory (LSTM) as it is, the time resolution was improved by successively classifying the states at that time, and the time lag problem due to the window function was solved. This is a framework of END to END learning aiming for deep learning in recent years. We report to verify the result of learning by using GPU and movement classification data of at least 100 healthy participants, in order to prevent from overfitting the model of deep neural network for training data as much as possible.

Disclosures: Y. Fujiwara: None. **S. Honda:** None. **J. Ushiba:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.12/MM12

Topic: E.05. Brain-Machine Interface

Support: National Key R&D Program of China
National Science Foundation of China
Shanghai Bureau of Science & Technology

Title: Decode predictive cortical activity for dynamic brain-machine interface

Authors: *H. CUI, C. LI, Y. ZHANG, T. WANG, X. XU, Q. WANG
Lab. of Neural Mechanism of Motor Control, Inst. of Neuroscience, CAS, Shanghai City, China

Abstract: Despite considerable advances in brain-machine interfaces (BMIs) over the past 20 years, it is still difficult to decode neural signals for predictive control of artificial actuators in response to dynamic stimuli. In contrast to naturalistic limb movements largely based on forward planning, most brain-controlled prosthetic systems largely rely on visual feedback without prior trajectory formation. In the present study, we recorded neuronal activity from the posterior parietal cortex and the motor cortex in rhesus monkeys performing center-out reaching arm

movement to intercept a target appearing at random locations and circularly moving with random speeds around the center of the touch-sensitive screen. Instead of a pre-defined zone, the monkeys might choose to intercept the moving target anytime within 1 s after its appearance. Our recent behavioral results demonstrated that manual interception could fully compensate for sensorimotor delays based on the forward prediction of the future target location at interception (Li et al. J Neurophysiol 2018). Although directional tunings of individual neurons appear to be heterogeneous and dynamic, a finite impulse response (FIR) Wiener filter based on regression analysis of neuronal population activity was built to decode pre-movement activity (750ms to 250ms prior to movement onset, ~40 neurons) and provide accurate (SD = 12º in movement direction) control signals for guiding BMI systems in dynamic environments.

Disclosures: H. Cui: None. **C. Li:** None. **Y. Zhang:** None. **T. Wang:** None. **X. Xu:** None. **Q. Wang:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.13/MM13

Topic: E.05. Brain-Machine Interface

Support: HFSP

Title: Decoding and modeling parietal cortex activity to probe representational drift

Authors: *A. LOBACK, D. RAMAN, T. O'LEARY
Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Understanding how local brain circuits are able to compute robustly despite ongoing spine dynamics and other processes is a fundamental challenge in neuroscience. At the population coding level, recent work from multiple groups has shown that neural population activity representing learned environments continually drifts, so that specific environmental variables are represented by different neuronal ensembles over days or weeks [1,2]. Here we take a data-driven and modeling approach to probe the nature of this representational drift in the parietal cortex. We analyze two-photon calcium imaging data of ensembles of hundreds of neurons in the posterior parietal cortex (PPC) recorded from mice performing a PPC-dependent cue-action association task in a virtual reality environment. We first show that two different linear dynamic models - a linear time-invariant model decoder with a latent state variable and a Kalman filter decoder - can be used to reliably decode multiple kinematic and behavioral variables from PPC ensemble activity. Concurrently, we explore an observer framework model of the PPC, a concept from control engineering, in which the PPC computes an internal prediction of the kinematic and environmental state. This modeling framework allows us to

explore questions about stochastic optimization algorithms that are consistent with the previously-observed activity drift in the PPC, and consequences within a larger network of coupled neural systems that are involving in learning.
References: 1. Ziv, Y., Burns, L.D., Cocker, E.D., Hamel, E.O., Ghosh, K.K., Kitch, L.J., El Gamal, A., and Schnitzer, M.J. (2013). Long-term monitoring of neuronal population activity. Nat. Neurosci., 16:264-266. 2. Driscoll, L.N., Pettit, N.L., Minderer, M., Chettih, S.N., Harvey, C.D. Dynamic Reorganization of Neuronal Activity Patterns in Parietal Cortex. Cell, 170(5):986-999.

Disclosures: A. Loback: None. **D. Raman:** None. **T. O'Leary:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.14/MM14

Topic: E.05. Brain-Machine Interface

Support: German Cluster of Excellence BrainLinks-BrainTools (EXC 1086)
Federal Ministry for Education and Research (13GW0053A-E)
Federal Ministry Economic Affairs and Energy (16KN022122)

Title: Brain interchange: A novel brain computer interface system

Authors: *J. RICKERT[1], M. SCHUETTLER[1,2], C. STOLLE[1], F. WENZEL[1], N. GRIGAT[1], F. KOHLER[1], M. OBERT[1], S. RIEGER[1], T. STIEGLITZ[2], T. BALL[2,3]
[1]CorTec GmbH, Freiburg, Germany; [2]BrainLinks - BrainTools, Univ. of Freiburg, Freiburg, Germany; [3]Neurosurg., Med. Ctr. - Univ. of Freiburg, Freiburg, Germany

Abstract: Treatments of neurological disorders utilizing active implantable devices which interact with the activity of the brain are demonstrating increasingly promising advances. Next to the continuous improvement of established therapies for movement disorders, Epilepsy and chronic pain, new therapies for depression, paralysis and many more are under investigation. The current technology available for the development of these treatments is derived from the first active implants, the cardiac pacemakers, developed in mid to late 20th century: battery powered devices with few channels and limited intelligence. The Brain Interchange technology, developed in a joint effort by the University of Freiburg and CorTec, is a new system, enabling battery-free, intelligent closed-loop applications with up to 32 channels in its first version. The implantable part, including a novel hermetic encapsulation, custom electronics and firmware, were presented last year. The electrode technology will be presented in a companion poster. Here we present the progress in the development of the external parts and the software of the system and discuss potential applications.

The first version of the external parts of the system manages power and communication with the implant, as well as the software for controlling the system. Physically, these parts consist of a head piece, a relay- and a controller unit. The main functions, accessible via a graphical user interface, are: managing recording and stimulation, measuring impedance and reading out humidity, temperature, supply voltage and unique ID of the implant. A filter pipeline for signal processing and feature extraction, suitable for computationally demanding closed-loop algorithms, and the control of external devices with minimal latency has also been implemented. For future collaboration partners programmable interfaces for C++, Matlab and Python are available. The development has been done under ISO-13485 and according to EN 62304. Potential applications range from closed-loop stimulation for the treatment of Parkinson's disease or Epilepsy to the control of assistive technology in chronic paralysis or for rehabilitation purposes. Further applications could lie in closed-loop treatments in the peripheral nervous system.

Acknowledgements:
Funding was supplied within the German Cluster of Excellence BrainLinks-BrainTools (EXC 1086), by the Federal Ministry for Education and Research (13GW0053A-E) and by the Federal Ministry Economic Affairs and Energy (16KN022122).

Disclosures: M. Schuettler: None. **C. Stolle:** None. **F. Wenzel:** None. **N. Grigat:** None. **F. Kohler:** None. **M. Obert:** None. **S. Rieger:** None. **T. Stieglitz:** None. **T. Ball:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.15/NN1

Topic: E.05. Brain-Machine Interface

Support: LBNL-internal LDRD

Title: Neuromorphic computing algorithms and hardware for low-power neural decoding and brain-machine interfaces

Authors: *D. G. CLARK[1], J. A. LIVEZEY[1], E. F. CHANG[2], K. E. BOUCHARD[1]
[1]Biosci., Lawrence Berkeley Natl. Lab., Berkeley, CA; [2]Neurosurg., UCSF, San Francisco, CA

Abstract: Decoding neural population activity is a ubiquitous task in systems neuroscience. A common application is brain-machine interfaces (BMIs), which restore lost function by mapping neural recordings to control signals in real-time. However, challenges remain in deploying such systems. For example, decoding algorithms are often computationally demanding and thus dissipate significant energy operating continuously. We address this problem by mapping the Kalman filter (KF) onto a low-power neuromorphic architecture: IBM's TrueNorth. The

resulting decoder consumes only ~10-100 mW of power running in real-time and reproduces the KF with high accuracy. In contrast to previous research, our decoder is run on actual neuromorphic hardware. We have also derived a full analytical model describing the error between the spiking KF and an equivalent non-spiking KF which we validate numerically. We demonstrate the utility of our decoder offline by decoding human vocal pitch from ECoG.
While several groups have raised the possibility of neuromorphic decoders, none have directly addressed the inherent tradeoffs imposed by a neuromorphic chip. Our work required us to encounter and address many fundamental limitations related to performing computations on spike trains in a streaming fashion. For example, in a neuromorphic architecture featuring spiking neurons, such as TrueNorth, data are typically encoded using a rate code (i.e. value = # spikes / time). This encoding scheme induces a tradeoff between numerical precision and latency. For real-time decoding, this tradeoff must be mitigated: the decoded signal must have reasonable numerical precision, ~10 bits, and the latency must be low, ~10-100 ms. We simultaneously achieve these requirements by introducing a method that reduces the latency of the system by increasing the number of neurons, while exactly preserving the computation performed. The ability to smoothly trade-off between latency and on-chip neuronal footprint widens the scope of applicability of spiking neuromorphic architectures.
Overall, our findings demonstrate that neuromorphic technology presents a promising and practical path forward for low-power, portable neural decoding.

Disclosures: D.G. Clark: None. **J.A. Livezey:** None. **E.F. Chang:** None. **K.E. Bouchard:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.16/NN2

Topic: E.05. Brain-Machine Interface

Title: A scalable closed-loop network of wireless implants with up to 128 channels of recording and stimulation

Authors: *C. A. SEGURA, J. G. HELLMAN, A. CZARNECKI, A. J. MIRANDA, M. C. MURESAN, E. H. GREENWALD, C. K. BJUNE, J. R. LACHAPELLE, J. R. BURNS, IV, B. D. NUGENT, D. J. GUYON, W. T. UY, C. J. WARDMAN, G. D. GRANT, T. S. SRIRAM, A. G. STODDARD, A. M. ZORN, J. J. WHEELER
Draper, Cambridge, MA

Abstract: Advanced close-loop neuromodulation systems aim to provide precision coordinated therapies across multiple distributed targets. Potential applications include neuropsychiatric illness, memory loss, sensorimotor restoration, pain management, bladder control, and more.

While communication between multiple neural targets is advantageous for coordinated therapies, networked lead wires and connectors add considerable bulk to the overall implanted volume. Here, we present our wirelessly networked Gemstone implant system that eliminates the need for lead wires and connectors and achieves a total implanted volume less than 1.5 cm^3. Each Gemstone implant is wirelessly powered by, and communicates with, a single external antenna module for coordinated closed-loop control of 32 channels each. As few as one, and as many as four Gemstones can be implanted for up to 128 electrodes for recording and stimulation. Each Gemstone can be re-configured on-the-fly for a variety of mixed recording and stimulation settings, including differential and single-ended recording, variable bandwidths and sampling rates, and arbitrary stimulus waveforms. Custom Draper ASICs provide low-noise recording (under 1µV RMS), precision stimulation (µA/µs resolution up to +/-9V compliance), and wireless data networking (20 Mb/s). Gemstone implants are packaged within a dime-sized biocompatible hermetic enclosure and can be mated with a variety of different electrode arrays for many uses.

Disclosures: C.A. Segura: None. **J.G. Hellman:** None. **A. Czarnecki:** None. **A.J. Miranda:** None. **M.C. Muresan:** None. **E.H. Greenwald:** None. **C.K. Bjune:** None. **J.R. Lachapelle:** None. **J.R. Burns:** None. **B.D. Nugent:** None. **D.J. Guyon:** None. **W.T. Uy:** None. **C.J. Wardman:** None. **G.D. Grant:** None. **T.S. Sriram:** None. **A.G. Stoddard:** None. **A.M. Zorn:** None. **J.J. Wheeler:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.17/NN3

Topic: E.05. Brain-Machine Interface

Support: NIH R21EY027570
NSF EAGER 1551239
DARPA HR0011-15-2-0006
McNight Foundation Technological Innovations in Neuroscience Award [JMC, MMM]
Chan Zuckerberg Biohub [MMM]

Title: A backscatter communication technique for distributed microimplantable wireless neural interfaces and implementation with neural dust

Authors: *D. K. PIECH[1,2], J. M. CARMENA[3,4,2], M. M. MAHARBIZ[3,2]
[1]Univ. of California Berkeley, Berkeley, CA; [2]UCB - UCSF Grad. Program Bioengineering, [3]EECS, [4]Helen Wills Neurosci., UC Berkeley, Berkeley, CA

Abstract: Microimplantable wireless neural interfaces are an emerging class of neural interfaces which consist of fully self-contained sensing or stimulating devices placed directly at electrophysiological recording or stimulation sites. A goal of these systems is to leverage extreme miniaturization, low power, and efficient communication to situate wireless interface devices in the tissue of interest, including intracerebral sites. Such microimplantable neural interfaces may reduce micromotion and gliosis, enable distributed recording and stimulation throughout the brain without cable management constraints, and present options for low-risk implantation, thus leading to improved safety, longevity, and channel count.
The neural dust platform utilizes ultrasound for power and backscatter communication via an acoustic wireless link between an external interrogator and implanted devices ('dust motes'). The acoustic link safely penetrates through tissue and scales to smaller implantable devices sizes as compared to a radio frequency (RF) wireless link. Some capabilities of RF systems, such as continuous wave and narrow band communication, though, are less viable with an acoustic link. This provides both challenges and opportunities toward designing a backscatter wireless link paradigm optimized for ultrasound.
We present a new pulse-backscatter communication technique designed to enable robust and flexible communication with a freely floating cloud of microimplantable neural sensors. Much of the processing burden of the link is transferred from the mote to the external interrogation system, keeping the motes as simple - and therefore small and low power - as possible.
We demonstrate (1) improved SNR as compared to baseline pulse-backscatter methods, (2) robustness to misalignment and drift motion of the acoustic link, (3) communication through an attenuating and scattering skull phantom, and (4) simultaneous communication with multiple motes.
These results show that a robust wireless link can be established while maintaining the small size and simplicity of the implanted devices. This paves the way toward the long-term goal of a distributed cloud of microimplantable neural sensors.

Disclosures: D.K. Piech: None. **J.M. Carmena:** A. Employment/Salary (full or part-time):; iota Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); iota Biosciences. **M.M. Maharbiz:** A. Employment/Salary (full or part-time):; iota Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); iota Biosciences.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.18/NN4

Topic: E.05. Brain-Machine Interface

Title: Technological challenges for large channel count, high bandwidth human brain-interface systems

Authors: *C. CLEMENT, T. L. LAABS, J. P. DONOGHUE
Wyss Ctr. for Bio and Neuro Engin., Geneve, Switzerland

Abstract: Interfacing a pulse generator, a recorder, or any implanted electronics, with the nervous system is very challenging, due to the fragile nature of the tissues, the immense complexity of the brain, the capture of tiny signals on hundreds of electrodes, and the large flow of information to be transferred in and out the body. In the cases where we want to have electrodes interfacing directly with the brain (subcutaneously, epi- or subdural, penetrating the cortex or deep brain stimulation), it is appropriate to locate the implanted electronics 'above the neck'. With the exception of cochlear implants, current neurological stimulators, like Deep Brain Stimulation for Parkinson Disease, are still too big. The pulse generator is then implanted in the pectoral area, with cables tunneled along the neck and under the scalp. Miniaturization and new encapsulation technologies make it possible to move the electronics in the head. The human head is a very special environment which imposes specific design constraints on implants. We describe the criteria that should be taken into account to optimize the design of 'above the neck' active implants, in the perspective of efficacy of the therapy and that also takes the needs of patients and doctors into consideration. The poster covers a broad spectrum of the new challenges induced by moving the implant technology above the neck, especially in terms of energy, size, material, fixation, aesthetics, reliability, connectivity, surgical insertion and wireless communication. Devices that interface with the brain usually include many channels for either reading signals or stimulating specific brain areas. Having more than 100 channels or electrodes creates new challenges especially in terms of connections. Compared to active implants placed in the chest and abdomen, 'above the neck' devices must adhere to different design rules. Several key building blocks, like hermetic feedthroughs or batteries, must be re-invented to meet the specificities of multi-channel wireless long term implanted brain interfaces. We focus on understanding the 'environment', including the physical specificities of the human head. A careful analysis of advantages and drawbacks of existing active implants used for many therapies and diagnostics in various places in the body will show us the direction to take for neuro-stimulators of the future. The Wyss Center for Bio and Neuroengineering, based in Geneva, Switzerland, is a non-profit translational organization that accelerates the development of neurotechnologies for human benefit.

Disclosures: C. Clement: None. **T.L. Laabs:** None. **J.P. Donoghue:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.19/NN5

Topic: B.09. Network Interactions

Support: NSF CAREER Award CCF-1453868

Title: A personalized closed-loop system for control of EEG under medically-induced coma

Authors: *Y. YANG[1], J. T. LEE[3,5], J. A. GUIDERA[3,5], K. Y. VLASOV[3,5], J. PEI[3,5], E. N. BROWN[3,5,6,4], K. SOLT[5,3,6], M. M. SHANECHI[1,2]
[1]Electrical Engin., [2]Neurosci. Grad. Program, USC, Los Angeles, CA; [3]Brain and Cognitive Sci., [4]Inst. for Med. Engin. and Sci., MIT, Cambridge, MA; [5]Anesthesia, Critical Care and Pain Med., Massachusetts Gen. Hosp., Boston, MA; [6]Anaesthesia, Harvard Med. Sch., Boston, MA

Abstract: Medically-induced coma, a profound brain inactivation state induced by administering anesthetics, is a critical therapy needed to be maintained for long periods of days in the intensive care unit. Personalized automatic control of the therapy could thus significantly improve the safety and efficacy of anesthesia care but has not yet been demonstrated. In current clinical practice, medically-induced coma is maintained manually by monitoring the electroencephalogram (EEG) burst suppression pattern. To enable personalized automatic control, both inter- and intra-subject variabilities in the EEG response to anesthetics need to be tracked in real time while simultaneously delivering the therapy, which is not possible in current control systems. Here, using an adaptive stochastic control framework, we develop a personalized closed-loop anesthetic delivery system for medically-induced coma that tracks both inter- and intra-subject variabilities in real time during closed-loop anesthetic delivery. We tested the personalized closed-loop system in a rodent model by administrating propofol to control the EEG burst suppression. The closed-loop system achieved precise control in each subject without a separate offline model fitting experiment, thus tracking inter-subject variability without therapy interruption. In addition, the closed-loop system tracked intra-subject variability, thus providing a tool to uncover how the EEG response to propofol changed during the course of control. Moreover, by tracking these intra-subject variabilities, the closed-loop system significantly reduced control bias and error. This personalized closed-loop anesthetic delivery system has significant implications for clinical feasibility of automated and personalized care in medically-induced coma and provides a new tool to investigate the dynamics of brain response to anesthetics.

Disclosures: Y. Yang: None. **J.T. Lee:** None. **J.A. Guidera:** None. **K.Y. Vlasov:** None. **J. Pei:** None. **E.N. Brown:** None. **K. Solt:** None. **M.M. Shanechi:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.20/NN6

Topic: E.05. Brain-Machine Interface

Support: This research was supported by the convergence technology development program for bionic arm through the National Research Foundation of Korea(NRF) funded by the Ministry of Science & ICT. (No. 2017M3C1B2085292)
This research was supported by Mid-career Researcher Program (NRF-2015R1A2A2A04005487) through the National Research Foundation of Korea(NRF) funded by the Ministry of Science & ICT.

Title: A low-invasive microcoil integrated neural probe for deep brain magnetic stimulation

Authors: *J. KIM[1], H. PARK[1,2], Y. HUH[3], J. CHO[3]
[1]KIST Korea Inst. of Sci. & Tech., Seoul, Korea, Republic of; [2]Sch. of Mechanical Engin., Yonsei Univ., Seoul, Korea, Republic of; [3]Catholic Kwandong Univ., Incheon, Korea, Republic of

Abstract: Although the conventional transcranial magnetic stimulation (TMS) method has the advantage of non-invasive stimulation, it is still unable to perform deep brain stimulation, simultaneous neural signal monitoring, stimulation of a specific region less than square centimeter, and repeatable stimulation of the same region due to the movements of the external system and the patient.
In this study, we propose a neural probe with microcoils and tetrode type electrodes capable of acquiring neural signals while simultaneously providing deep brain magnetic stimulation. It has more focused and efficient stimulation performance than the conventional TMS system. Unlike the conventional probes with monolayer microcoils that have been studied in the past, we propose a single neural probe integrated with three-layered microcoil for magnetic stimulation and tetrode-type electrodes capable of real-time neural signal acquisition.
In order to verify the applicability, the Finite Element Analysis (FEA) was used to confirm the electromagnetic field distribution and intensity according to the depth of the magnetic field generated by the three-layered microcoil model. Microcoil design parameters were set based on the result, and the proposed device was fabricated with micro-fabrication technologies.
To apply various types of magnetic stimulation patterns such as iTBS and cTBS using the microcoil integrated in the neural probe, an external stimulation system was developed that consists of a function generator, a power supply, an amplifier, and a control software based on Labview program. The developed software consists of a stimulation control panel and a stimulation cycle control panel. The stimulation control panel was designed to set the type, frequency, current size, and duty cycle of the stimulation signal waveform individually. The stimulation cycle control panel was made to adjust the signal waveform to stimulate at regular intervals.
The proposed monolithic neural probe for magnetic stimulation overcame the size and configuration limitations of the conventional microcoil based magnetic stimulation systems or neural probes. This specific and selective magnetic stimulation would be beneficial to study the mechanism of brain stimulation in various regions of the brain, such as the, the Brain-Computer Interface (BCI) that require precise activation of specific regions in the brain, and could further be applied to clinical uses in the future.

Disclosures: **J. Kim:** A. Employment/Salary (full or part-time):; Korea Institute of Science and Technology. **H. Park:** None. **Y. Huh:** None. **J. Cho:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.21/NN7

Topic: E.07. Rhythmic Motor Pattern Generation

Title: The possibility of low TMS field for neuronal stimulation

Authors: *H. BAGHERZADEH[1], Q. MENG[1], X. DU[2], L. HONG[2], F.-S. CHOA[1]
[1]Computer Sci. and Electrical Engin. Dept., Univ. of Maryland, Baltimore County, Baltimore, MD; [2]university of Maryland school of Medicine,MPRC, Baltimore, MD

Abstract: In recent years, a variety of non-invasive techniques of neuronal stimulation such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCs) and transcranial alternating current stimulation (tACs) have been developed. The development of these techniques has opened new horizons for the treatment of neuropsychiatric diseases like depression, Obsessive Compulsive Disorder (OCD), Alzheimer, Schizophrenia, etc. The neuronal stimulation in TMS requires electric fields near 400 V/m to reach activation threshold while in tACs and tDCs, the strength of the applied field hardly passes 1 V/m. In the current study, the reasons behind this phenomenon are investigated among which duration of applied magnetic field is of importance. The effects of short period application of TMS is compared with that of longer period applications of tACs and tDCs, in terms of charging up the membranes of targeted neurons and reaching threshold. The possibility of having lower TMS field but running at longer duration has the potential to greatly reduce TMS system size, cost, and portability. For this purpose, the mechanisms of these neuronal stimulation techniques were thoroughly studied. The induced electric field upon the nerve is governed using a cable model containing Hodgkin-Huxley model elements considering both Lorentz and Coulomb gauges.

Disclosures: H. Bagherzadeh: None. **Q. Meng:** None. **X. Du:** None. **L. Hong:** None. **F. Choa:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.22/NN8

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant U01 NS098976-01
NIH Grant P50-MH109429
NYSDOH ECRIP Fellowship

Title: Frequency specific effects of direct intracranial electrical stimulation in the human brain

Authors: *S. BICKEL[1], J. L. HERRERO[2,3], E. M. YEAGLE[3,2], M. R. MERCIER[4], S. KHUVIS[2,3], P. LAKATOS[5], A. D. MEHTA[2,3]
[1]Neurosurg. / Neurol., [2]Neurosurg., Hofstra Northwell Sch. of Med., Manhasset, NY; [3]Feinstein Inst. for Med. Res., Manhasset, NY; [4]CNRS, Toulouse, France; [5]Nathan Kline Inst., Orangeburg, NY

Abstract: Direct intracranial electrical EBS stimulation (iEBS) is a fast developing technology, which already has clinical applications in epilepsy, select movement, and neuropsychiatric disorders. Traditionally used paradigms with open-loop, high frequency, high amplitude stimulation do not take ongoing network dynamics into account and likely disrupt them. However, such, often rhythmic dynamics have been implicated in processes from motor preparation and execution to cognitive processes such as attention. Developing novel iEBS paradigms to systematically modulate rhythmic neuronal activity patterns or neuronal oscillations may provide a promising approach to not only causally test their mechanistic significance but ideally also provide novel iEBS based therapeutic approaches.
Since little is known about the degree to which ongoing oscillations can be modulated by iEBS in humans, in the current study, we applied rhythmic electrical stimulation protocols covering several frequency bands to selected cortical regions (pre-central, superior temporal, parietal). Our goal was to test if we could achieve stimulation frequency specific effects in the stimulated and connected brain areas in epilepsy patients being evaluated with intracranial electrodes for seizure onset localization. We repeatedly applied brief bursts (<2secs) of low amplitude (0.5 - 3mA) electrical pulses (<0.4msec) through electrodes implanted in the frontal, temporal, and parietal regions. We stimulated in a closed-loop approach at different frequencies centered around the prominent spectral peaks of the activity in the targeted brain areas, as well as open-loop at a wider range of frequencies. We found that this rhythmic, low amplitude stimulation can indeed entrain neuronal oscillations. Notably, the effects outlasted the electrical stimulation in a frequency specific manner. These findings may help to develop iEBS paradigms paired with

sensory stimulation in behavioral experiments to elucidate the mechanistic roles of neuronal oscillations.

Disclosures: S. Bickel: None. **J.L. Herrero:** None. **E.M. Yeagle:** None. **M.R. Mercier:** None. **S. Khuvis:** None. **P. Lakatos:** None. **A.D. Mehta:** None.

Poster

672. Brain-Machine: Technical Development and Theory

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 672.23/NN9

Topic: I.07. Data Analysis and Statistics

Support: Life Science Research Foundation

Title: Real-time convolutional compressed sensing enables online spike recovery from high-density electrode recordings with inherent overlap resolution

Authors: *S. WEINGÄRTNER, X. CHEN, T. MOORE
Stanford Univ. and Howard Hughes Med. Inst., Stanford, CA

Abstract: Extracellular electrophysiological recordings from single neurons have been instrumental for much of our present understanding of functioning neural circuits, particularly in behaving animals. Recent advances have facilitated the fabrication of electrodes with 100s of channels, potentially revolutionizing electrophysiology by enabling population scale recordings (Jun et al. 2017). However, while this advancement was driven by hardware development, multi-electrode recordings pose new challenges for the post processing and analysis of data with spike sorting, especially in terms of resolution of overlapping spikes and computational efficacy (Lefebvre et al. 2016). In this work, we apply concepts of sparse signal processing to study online spike detection, a problem that is highly relevant for closed loop neuroscience and brain-machine interfaces (Fetz 2007). We use a generative model describing the extracellular recording as a linear sum of waveform templates convolved with spike times and pose a sparsity assumption on the spiking activity (Ekanadham et al. 2014). This characterization inherently enables the resolution of spatio-temporal overlap. We employ the results of Demko, Moss and Smith on banded matrices (Demko et al. 1984), to demonstrate that accurate signal recovery can be performed in an online setting by processing finite buffers, despite continuously updated measurements. To achieve practical buffer sizes we improve upon the classic results, by characterizing the error propagation in the linear system using Neumann series expansion, allowing for partial decoupling of the subproblems. We propose an adaptation of the CoSAMP method (Needell et al. 2008) to enable online processing. Iterative processing is restrict to a buffer whose size is continuously updated based on the results of the Neumann series. Noisy, ground-truth simulations using waveform templates from recordings in the macaque visual

cortex reveal negligible performance difference between the proposed algorithm with online and batch (i.e. all data available at once, prohibitive for online use) processing (noisefree: $p = 0.32$, noisy: $p = 0.14$). Good resolvability of overlapping spikes is achieved in application to real data from trodal recordings, with increased performance when waveforms are present on multiple channels. In conclusion we demonstrate that greedy sparse signal recovery with limited buffer size enables efficient and accurate online spike detection. In combination with offline waveform extraction from an initial training phase, this provides a means for using single-neuron spiking activity in closed loop experiments.

Disclosures: S. Weingärtner: None. **X. Chen:** None. **T. Moore:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.01/NN10

Topic: E.06. Posture and Gait

Support: VR(M) Grant 2017-02944
VR(M) Grant 21076

Title: Role of nucleus reticularis gigantocellularis in control of posture

Authors: P. V. ZELENIN, M. D. G. VEMULA, V. F. LYALKA, *T. DELIAGINA
Karolinska Inst., Stockholm, Sweden

Abstract: Terrestrial quadrupeds actively stabilize dorsal side up orientation of the body in space due to activity of the closed-loop postural control system. It consists of three relatively independent subsystems, stabilizing orientation of the head, anterior and posterior parts of the trunk, respectively. Supraspinal influences play a crucial role in operation of these sub-systems. The aim of the present study was to reveal the role of supraspinal signals originating from nucleus reticularis gigantocellularis in operation of sub-systems stabilizing the body orientation in space. For this purpose, effects of DREADD-based chemogenetic activation and inactivation of all neurons, as well as only CaMKIIα glutamatergic neurons in nucleus reticularis gigantocellularis on different aspects of postural control, were studied. Wild type mice were trained to stand still on a platform, which was subjected to left-right lateral tilts with the amplitude ±20º. Tilts of the platform caused postural corrections moving the dorso-ventral axis of the head and trunk toward the vertical. Then the mice were subjected to a virus injection into nucleus reticularis gigantocellularis unilaterally. To target all neurons, AAV5-hSyn-hM3D(Gq)-mCherry or AAV5-hSyn-hM4D(Gi)-mCherry was injected, while to target CaMKIIα glutamatergic neurons only, AAV5-CaMKIIα-hM3D(Gq)-mCherry or AAV5-CaMKIIα-hM4D(Gi)-mCherry was injected. In two weeks after the injection, the animals with markers on

hindlimb joints and spine were video recorded from the front and back (when standing on a horizontal platform, as well as during its lateral tilts) before and during chemogenetic activation/inactivation of infected reticular neurons (in 1 hour after CNO injection). We found that unilateral activation of all reticular neurons in nucleus reticularis gigantocellularis, as well as only CaMKIIα glutamatergic reticular neurons, evoked ipsilateral, while their inactivation - contralateral roll tilt of the head and trunk in animals standing on the horizontal platform. The asymmetrical (tilted) orientation was actively stabilized on the tilted platform. We found that the efficacy of postural corrections was similar before and after CNO injection. Thus, left-right asymmetry in activity of neurons located in nucleus reticularis gigantocellularis caused a shift of the equilibrium point of the postural control sub-systems stabilizing the head and trunk orientation in the transverse plane, but did not affect the efficacy of the postural corrections. Most likely this shift is caused by left-right asymmetry in activity of reticulospinal neurons.

Disclosures: P.V. Zelenin: None. **M.D.G. Vemula:** None. **V.F. Lyalka:** None. **T. Deliagina:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.02/NN11

Topic: E.06. Posture and Gait

Support: NSERC Grant RGPIN-2017-04175

Title: Cutaneous reflexes from the hand are influenced by the reliability of a light touch reference during standing

Authors: A. J. MCMAHON[1], H. HACKETT[1], J. KRUTZ[1], *J. E. MISIASZEK[1,2,3]
[1]Univ. of Alberta, Edmonton, AB, Canada; [2]Occup. Therapy, Fac. of Rehabil. Med., Edmonton, AB, Canada; [3]Neurosci. and Mental Hlth. Inst., Edmonton, AB, Canada

Abstract: Light touch of a stable reference reduces sway during standing. Moreover, unexpected displacement of a light touch reference leads to short-latency reactions in ankle muscles consistent with a balance reaction. However, these responses were only observed following the first displacement, replaced by responses in arm muscles on subsequent trials. Thus, balance-related touch feedback can be quickly repurposed in a context-dependent manner, such as when the touch reference becomes unstable. We anticipate that sensorimotor pathways arising from finger cutaneous afferents would reflect these changes in behavior. In this study, we tested inter- and intralimb cutaneous reflexes arising from median or radial nerve stimulation while participants touched a stable reference and after the touch reference became unreliable. We hypothesized that 1) interlimb reflexes derived from median nerve stimulation would be

facilitated when touch was stable, but reduced when touch was unreliable, 2) intralimb median nerve reflexes would be facilitated when touch was unreliable and participants tracked the touch reference with arm movements, and 3) radial nerve evoked reflexes would be unaffected, given that the radial nerve innervation territory is not involved in the light touch task. Cutaneous reflexes were recorded from arm and leg muscles with median (n = 12) or radial (n = 11) nerve stimulation during each of three conditions: standing on foam with eyes closed a) without touch, b) while lightly touching (< 1N) a stable reference, and c) touching a reference that has been unexpectedly and repeatedly displaced. Median nerve evoked interlimb reflexes recorded in soleus (SOL) were significantly ($p<0.05$) larger when touching the stable reference (mean ± sd %MVC; 4.78 ± 1.31) than when not touching a reference (1.00 ± 1.05) or when touching an unstable reference (1.07 ± 1.16). Median nerve reflexes in other leg muscles were not different. Median nerve evoked intralimb reflexes in anterior deltoid (AD) were significantly ($p<0.05$) larger when touching an unstable reference (4.50 ± 1.31), compared to touching a stable reference (1.34 ± 1.01) or not touching (1.50 ± 1.00). Median nerve reflexes in other arm muscles were not different. In contrast to the median nerve evoked reflexes, radial nerve evoked interlimb reflexes in SOL were significantly ($p<0.05$) larger when not touching (4.29 ± 4.34), compared with touching a stable (1.50 ± 2.78) or unstable reference (2.30 ± 4.01). Radial nerve reflexes in other muscles were not different. These findings indicate that light touch influences the excitability of sensorimotor pathways depending upon the relevance of the contact to balance control.

Disclosures: A.J. McMahon: None. **H. Hackett:** None. **J. Krutz:** None. **J.E. Misiaszek:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.03/NN12

Topic: E.06. Posture and Gait

Support: Jeffress Memorial Trust

Title: The nociceptive withdrawal response in intact, unanesthetized rats preserves postural stability over accuracy

Authors: *C. L. CLELAND, Y. KIM, K. M. SAMMONS, G. VERDI, C. A. CHRZAN, K. SEAMON
Biol., James Madison Univ., Harrisonburg, VA

Abstract: The nociceptive withdrawal response (NWR) is a protective movement in response to noxious stimuli in which multi-joint rotation rapidly removes the affected limb or appendage. However, recent work from our laboratory has shown that the direction of withdrawal either does

not depend (Cleland et al., unpublished observations) or depends weakly (Cleland & Bauer 2002, Cleland et al. 2017) on stimulus location, raising the question as to what factors determine withdrawal direction. Given that a strong, rapid NWR may destabilize posture, the goal of our experiments was to explore the role of posture on the NWRs of the foot and tail in response to noxious heat stimuli. The NWR was evoked by noxious heat created from laser (980nm) stimulation applied to the plantar surface of the paw and along the lateral aspect of the tail in intact, unanesthetized Sprague-Dawley rats (n=131). The resulting movement was recorded with conventional (60 fps) and high speed (650 fps) video. The initial posture was varied by either positioning the tail at different angles or curvature, positioning the foot at various rostral/caudal locations, or depending on the spontaneous positioning of the rat foot. Heat stimulation uniformly evoked brisk withdrawal responses in various directions. For both the foot and the tail, the response direction varied with initial placement of the appendage. For the foot, there was an inverse dependence on initial position. For example, if the foot were placed relatively rostral the movement was relatively caudal. For the tail, the direction of rotation around the base of tail reversed direction for large angles or curvature of the tail, directing the tail back toward a straight posture. In both model systems, the NWR served to minimize deviations from "normal" (tail straight, hind foot aligned with the opposing hind foot), thus potentially improving postural stability and allowing the greatest possible number of secondary movements. Combined with classic descriptions of the crossed extension reflex and more recent accounts of postural aspects of the NWR (Blivis et al. 2017), our results suggest that the quantitative characteristics of the NWR may have evolved in response to the need for postural stability rather withdrawal movement accuracy.

Disclosures: C.L. Cleland: None. **Y. Kim:** None. **K.M. Sammons:** None. **G. Verdi:** None. **C.A. Chrzan:** None. **K. Seamon:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.04/NN13

Topic: E.06. Posture and Gait

Support: NSERC Grant RGPIN-2017-04175

Title: Synaptic coupling of median nerve cutaneous afferents with ankle muscle motor pools

Authors: *A. TOTH[1], K. K. FENRICH[2], K. E. JONES[3], J. E. MISIASZEK[2,1]
[1]Dept. of Occup. Therapy, [2]Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada; [3]Fac Kinesiology, Sport, and Recreation, Univ. Alberta, Edmonton, AB, Canada

Abstract: Lightly touching a stable reference point can greatly improve balance. Unexpected displacement of a light touch reference at the finger can lead to rapid activation of ankle muscles in standing participants. Percutaneous electrical stimulation of the median nerve generates short latency reflexes in the muscles of the legs, suggesting that cutaneous afferents from the hand are functionally coupled with the ankle muscles and might be involved in generating these interlimb responses. In the present study, we wished to delineate the specific tactile afferents from the hand that might mediate these interlimb responses. Specifically, we hypothesized that activity of individual cutaneous afferents of the median nerve will modulate the electromyographic (EMG) activity of ankle muscles. To do so, microneurography of the median nerve at the level of the wrist was used to record from single afferents from 10 participants. Discharge from discretely resolved afferents was used for generating spike-triggered average surface EMG traces of the bilateral tibialis anterior (TA) and soleus (SOL) muscles. Single units were characterized as slow or fast adapting type I and II afferents (SAI, SAII, FAI, FAII) and their receptive fields were mapped. SA units were activated by applying a constant pressure, and FA units via gentle tapping, within their receptive fields. Participants were seated comfortably in a reclined chair and asked to maintain a 50% maximal voluntary contraction (MVC) of plantarflexion or dorsiflexion during tactile unit activation. At all other times, participants were asked to remain completely relaxed and minimize movements. Responses in the spike-triggered average EMG traces were identified when the trace exceeded a 99% confidence band, calculated from the background EMG activity, for a minimum of ≥ 2.5 ms. The background EMG activity was calculated from 50 ms prior, and 40 ms post, spike onset. Over 14 experiments, 17 single units were recorded, including: 4 FAI (24%), 1 FAII (6%), 6 SAI (35%), 4 SAII (24%), with 2 ectopic units (12%). Three latency epochs were used, early (40-80 ms), middle (80-120 ms), and late (>120 ms). In TA there were 13 early, 7 middle, and 16 late responses that met significance criteria, and in the SOL there were 5 early, 8 middle, and 13 late. These data demonstrate that activity from single mechanoreceptors of the hand are coupled to motoneuron pools of ankle muscles. The short-latency of some of these connections suggests that sensory input from the hand is capable of quickly adapting motor activity in the legs, which would be functionally important for stabilizing balance.

Disclosures: A. Toth: None. **K.K. Fenrich:** None. **K.E. Jones:** None. **J.E. Misiaszek:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.05/NN14

Topic: E.06. Posture and Gait

Title: Revealing abnormal lower-limb reflex couplings in post-stroke gait using H-reflex stimulation

Authors: *J. S. SULZER[1], T. AKBAS[1], K. MANELLA[2], R. K. LEE[3]
[1]Mechanical Engin., Univ. of Texas at Austin, Austin, TX; [2]Col. of Rehabilitative Sci., Univ. of St. Augustine for Hlth. Sci., Austin, TX; [3]St. David's Med. Ctr., Austin, TX

Abstract: It is widely believed that hip circumduction during gait is a compensatory strategy for reduced swing-phase knee flexion angle in people with post-stroke Stiff-Knee gait (SKG). However, our previous work refutes this hypothesis. In one study, we showed that alleviating the supposed cause of circumduction using robotic knee flexion assistance did not improve circumduction, but instead exaggerated it. These observations suggest an abnormal neuromuscular coupling between quadriceps and abductors in those with post-stroke SKG. In a follow-up study, we used musculoskeletal modeling and simulation to explore which muscles may have been involved in this abnormal coupling. We found that rectus femoris (RF) and gluteus medius (GMed) to be the most likely candidates. Yet this model requires experimental validation, and mechanical knee flexion assistance during gait can produce confounding effects including palpitation, coupled torques on other joints, and increased weight on the limb of the robotic orthosis. As such, in this study we employ electrically-induced reflexes in the RF using H-reflex stimulation of the femoral nerve in people with post-stroke SKG and age-matched healthy controls. We have developed a framework to consistently elicit quadriceps H-reflexes during walking and standing postures with and without increased voluntary RF contraction for healthy controls by providing RF EMG measures as feedback in real-time. Following RF H-reflex recruitment curves, we stimulated the RF at the peak H-reflex amplitude during a standing posture. We also stimulated RF during treadmill walking at toe-off walking at 0.5 m/s. We measured RF, GMed, tensor fascie latae, medial hamstrings, adductor longus, and vastus medius EMG during stimulation as well as 3D kinematic data during gait. Our preliminary analyses indicate increased RF H-reflex response and increased corresponding abductor EMG response following electrical stimulation in participants with post-stroke SKG compared to healthy controls. We are continuing to acquire additional data and perform additional analysis to derive more robust conclusions. Whereas our earlier evidence points out that hip circumduction in post-stroke SKG is not due to compensatory motions, this study helps define whether abnormal reflex mechanisms during gait could be the driving force behind this phenomenon.

Disclosures: J.S. Sulzer: None. **T. Akbas:** None. **K. Manella:** None. **R.K. Lee:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.06/NN15

Topic: E.06. Posture and Gait

Support: GT is supported by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie (grant agreement No 661452)
NIH R01EB007615 through NIBIB, NINDS, and NICHD
Christopher & Dana Reeve Foundation
Walkabout Foundation

Title: Electrophysiological window into the neuromodulation of the functional dynamics of spinal sensorimotor networks

Authors: *G. TACCOLA[1], S. CULACLII[2], P. GAD[3], H. ZHONG[4], N. KOKIKIAN[3], R. M. ICHIYAMA[6], W. LIU[2], V. EDGERTON[5]
[1]Dept. of Neurosci., SISSA, Trieste, Italy; [2]Dept. of Bioengineering, [3]Dept. of Integrative Biol. and Physiol., [4]Integrative Biol. and Physiol., [5]Dept Integrative Biol. & Physiol., UCLA, Los Angeles, CA; [6]Univ. Leeds, Leeds, United Kingdom

Abstract: Continuous, tonic electrical stimulation of the spinal cord at motor sub-threshold levels can neuromodulate spinal sensorimotor networks to physiological states, which enable human subjects clinically diagnosed with complete paralysis to generate voluntarily controlled movement. A series of sub-threshold electrical pulses delivered directly to the spinal cord through epidural electrodes can also evoke intrinsically variable reflex responses. This effect impacts the spinal cord in such a way that each effective amplitude during the successive stereotyped input train is unpredictably affected, including occasionally failing to generate a response. Weak pulses were applied directly through a sophisticated epidural micro-scaled electrode array, which is chronically implanted in the lumbosacral spinal cord and continuous EMG recordings were collected from awake intact rats at rest. The pulses elicited a rhythmically modulated motor output measured from bilateral hind-limb muscles. A similar pattern of rhythmic modulation is evoked even after an incomplete spinal cord injury that impairs both the descending drive from the cortex and locomotion. Under full anesthesia, in both intact and injured spinal cords, spontaneous rhythmic modulation decreased, resembling a stochastic profile that likely reflects a random basal modulation provided by propriospinal circuits. These results suggest that this stochastic signal might be an intrinsic feature of the neuromotor system, which can be exploited by an asynchronous stimulation pattern (Dynamic Stimulation), which induces motor output resonance. In addition, the novel epidural interface used in the present study demonstrates the ability to electrophysiologically monitor the dynamics of multiple motor pool-specific spinal networks in vivo and trace changes in spinal motor pool connectomes post-injury, with and without anesthetics. The existence of a spontaneous pattern of modulation of the motor output has important practical implications for spinal cord neuromodulation at low intensity and should be considered into the design of more effective neurorehabilitation protocols for persons living with a spinal cord injury.

Disclosures: G. Taccola: None. **S. Culaclii:** None. **P. Gad:** Other; he holds shareholder interest in NeuroRecovery Technologies and holds certain inventorship rights on intellectual property licensed by The Regents of the University of California to NeuroRecovery Tech. **H. Zhong:** None. **N. Kokikian:** None. **R.M. Ichiyama:** None. **W. Liu:** None. **V. Edgerton:** Other; he holds shareholder interest in NeuroRecovery Technologies and holds certain inventorship rights

on intellectual property licensed by The Regents of the University of California to NeuroRecovery Tech.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.07/NN16

Topic: E.06. Posture and Gait

Support: NSERC R6P1N-2015-0871
NSRIT #33817
CFI #33817

Title: Inhibitory pathway specifically modulated in the contralateral leg during walking

Authors: *O. D. LAFLAMME, T. AKAY
Dalhousie Univ., Halifax, NS, Canada

Abstract: Sensory afferents play an important role in coordinating the movement of multiple joints within and between legs during locomotion, as removal of sensory feedback severely impairs locomotion. It has been established in cats that sensory information from one leg influences the motor neuron (MN) activity of the contralateral leg (crossed reflex) through spinal commissural interneurons (CINs). Experiments in humans have shown that similar pathways exist since sensory stimulation can evoke motor responses in the contralateral leg. However, the neural circuits transmitting sensory afferents to the contralateral side of the spinal cord remains poorly understood. Experiments with mice revealed that left-right motor coordination is controlled by at least two genetically distinct classes of CINs (V0 and V3). Despite the insights regarding V0 and V3 involvement in locomotor activity, the role of these CINs in crossed reflexes remains unknown. Recently, crossed reflex pathways have been shown in mice *in vitro (Jiang et al, 1999, Brain Res, 816:493) and in vivo (Nakanishi and Whelan, 2012, J Neurophysiol, 107:500)* by applying a moderately strong toe pinch suggesting that crossed reflex pathways are also present in mice. Our goal is to characterize crossed reflex pathways in fully awake mice *in vivo* and investigate the involvement of different CINs implicated in walking in the transmission of sensory information to the contralateral side. Here, we describe crossed reflex motor output after the contralateral stimulation of cutaneous and proprioceptive afferents (tibial nerve stimulation), or only cutaneous afferents (sural nerve stimulation). The electromyogram (EMG) activity of different flexor and extensor muscles in the contralateral leg will be recorded simultaneously while adults mice are resting or walking *in vivo*. In summary, our data shows 1) that crossed reflex responses can be evoked in freely behaving mice in both flexor and extensor muscles following proprioceptive and cutaneous afferent stimulation; 2) that sensory information is transmitted to contralateral motor neurons through an inhibitory and

excitatory pathway, where the inhibitory influence is most likely mediated by cutaneous afferents; and 3) that crossed reflexes in mice are subject to modulation depending to the activity of the muscle prior to stimulation during walking. These experiments will serve as ground work in the mouse model to identify specific CIN pathways involved in crossed reflexes and the role of these crossed reflex pathways during motor behaviour. In the future we aim to assess the involvement of V3 and V0 CINs in crossed reflex.

Disclosures: O. D. Laflamme: None. **T. Akay:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.08/OO1

Topic: E.06. Posture and Gait

Support: NSERC Grant 400723

Title: Stochastic resonance effects in mechanically-evoked cutaneous reflex responses

Authors: *T. SHARMA[1], R. M. PETERS[2], L. R. BENT[1]
[1]Human Hlth. and Nutritional Sci., Univ. of Guelph, Guelph, ON, Canada; [2]Fac. of Kinesiology, Univ. of Calgary, Calgary, AB, Canada

Abstract: During stance, cutaneous mechanoreceptors sense pressure distribution across the foot sole and generate reflexes to modulate lower-limb muscle activity to successfully maintain upright balance. Decreased cutaneous reflex generation has been proposed to contribute to increased fall risk in populations such as the elderly. Therefore enhancing the generation of these reflexes may be a method of improving standing balance in these populations. A possible mechanism of enhancing cutaneous reflexes is through stochastic resonance (SR), which is a phenomenon where the detection of a signal is enhanced by the addition of subthreshold noise. SR-mediated enhancements have been shown in many neurophysiological systems such as tactile stimulus detection but have yet to be explored in cutaneous reflexes. Therefore, this study was conducted to explore the possibility of enhancing mechanically-evoked cutaneous reflex responses by introducing an electrical noise component to the system. Vibrotactile (input used to evoke a reflex) and electrotactile (noise component) stimuli (both Gaussian in nature, bandwidth: 0 - 50 Hz) were applied to the plantar skin at the heel of 11 young, healthy subjects (mean age = 20.9 years, SD = 1.14). The vibration intensity was 10 times perceptual threshold (PT) while electrotactile noise intensity varied between 0 and 100% of PT. Electromyography recordings were taken from the soleus (SOL), tibialis anterior (TA) and both medial (MG) and lateral gastrocnemius (LG). Cutaneous reflexes were quantified by measuring the peak to peak amplitude (PTP) of the cumulant density plot at each noise intensity for each subject. When

averaged across all subjects, no statistically significant differences were found in PTP across noise intensities in any muscles (SOL: p=0.091 MG: p=0.45, LG: p=0.42, TA: p=0.24). Separation of subjects based on their response to noise-mediated enhancements of SOL reflex (responders: n=6, non-responders: n=5), resulted in significant differences in SOL mean PTP of non-responders (p=0.028), while approaching significance in responders (p=0.059). No significant differences were observed in other muscles for both groups. Therefore, we conclude that trends of noise-enhancements of cutaneous reflexes may be observed in a subset of the population. In the rest of the population, noise seems to decrease cutaneous reflex generation. This information may help inform the design and application of biomedical aids to improve balance in clinical populations.

Disclosures: T. Sharma: None. **R.M. Peters:** None. **L.R. Bent:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.09/OO2

Topic: E.06. Posture and Gait

Title: Whole body vibration: Effects on soleus and flexor carpi radialis h-reflexes in healthy subjects

Authors: *M. M. SABBAHI[1], F. OVAK BITTAR[2]
[1]Texas Electrophysiology and Physical Therapy, Houston, TX; [2]Texas Physical Therapy and Rehab, Houston, TX

Abstract: Whole body vibration (WBV) has more frequently been utilized with athletic training. It was claimed that WBV increases the strength of healthy subjects. The WBV's physiologic effect on reflex functions has not been thoroughly evaluated. Tendon vibration is known to be a strong stimulus to Ia afferents causing tonic vibration reflexes. This presentation discusses the effect of WBV on Soleus and flexor carpi radialis (FCR) H-reflexes in healthy subjects. Subjects were tested for the Soleus and FCR H-reflexes using the method of Sabbahi & Khalil (1990). Surface electrodes were applied on the Soleus and FCR muscles while electrically stimulating the tibial and the median nerve (1 ms. pulses at 0.2 Hz at H-max). Recording parameters were 500 µv. /div., 10 Hz-1000 Hz bandwidth. Subjects were tested in standing (Soleus) and sitting (FCR) to evaluate the WBV effect on H-amplitude. WBV;11.6 vibration trainer of Freemotion inc. was used to elicit the vibration at 30- 50 Hz. at low or high amplitude for a period of 90 sec. H-reflexes were tested before and after different combinations of vibration frequencies and amplitude (low or high). Soleus H-reflex was tested during neutral stand, tiptoe, heel stand or during knee squat. FCR H-reflex was tested in sitting with hand rested on the vibration plate, or in wrist extension position. Five H-reflex traces were averaged for each trial with 3 min rest in

between trials. The peak-to-peak amplitude and reflex and muscle latencies were measured. Results showed H-amplitude inhibition for both the Soleus and FCR muscle (50-70% for Soleus & 30-40 % FCR)amplitude was substantially facilitated, during rest, post vibration for the Soleus and FCR muscles (10-20% for Soleus and 10-15% for the FCR). Tiptoe standing resulted in facilitation in the Soleus H-reflex. Heel standing and knee flexion resulted in complete H-reflex inhibition. Both maneuvers showed the minimal effect of vibration. Three minutes of continuous vibration of different frequencies and amplitudes resulted in Soleus H-reflex inhibition post-vibration. No measurable changes were recorded in the H or M-latencies. These results indicate a strong inhibitory effect on the motoneurone excitability of the lower and upper limbs, possibly due to a barrage of afferent pathways signal. The post-vibration facilitation indicates an increased excitability of the motoneurons pool that might be longer lasting. Such effect may result in the observed increase in the muscle strength recorded by studies in athletes and might be useful in rehabilitation of patients with neuromuscular disorders.

Disclosures: M.M. Sabbahi: None. **F. Ovak bittar:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.10/OO3

Topic: E.06. Posture and Gait

Support: NIH NICHD grant K01HD079584
NIH NICHD grant K12HD055931

Title: Influence of inter-stimulus intervals on transcranial magnetic stimulation-conditioning of soleus H-reflexes

Authors: *J. XU, A. LOPEZ, M. HOQUE, M. BORICH, T. KESAR
Dept. of Rehabil. Med., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Objective: Paring sub-threshold transcranial magnetic stimulation (TMS) with peripheral nerve stimulation (PNS) at specific inter-stimulus intervals (ISIs) can result in modulation of the Hoffman's reflex (H-reflex). Short latency facilitation (SLF) of the H-reflex is elicited by activation of a direct, fast-conducting descending corticospinal projections to the spinal lower motor neuron (LMN) when TMS is applied 1-5 ms after PNS. Long-latency facilitation (LLF) measures the excitability of indirect, polysynaptic, slower-conducting descending corticofugal pathways when TMS is applied 10 ms before PNS. However, the influence of ISI on the magnitude of TMS-facilitation of H-reflexes has not been systematically investigated. The purpose of this study was to investigate how varying the interval between the cortical and peripheral stimuli affects short- and long-latency TMS-conditioned H-

reflexes.Method: Ten able-bodied, young adult individuals participated this study. Sub-threshold TMS (90% active motor threshold, or AMT) was delivered at different stimulus intervals relative to electrical stimulation of tibial nerve. The ISI between the PNS and sub-threshold TMS was varied from -6 to +12ms. Negative ISIs indicate that the PNS was delivered prior to TMS, while positive ISIs indicate that PNS occurred after the TMS. We plotted the relationship between ISI and the amplitudes of conditioned H-reflexes at each ISI normalized by unconditioned H-reflexes.Results and Discussion: The mean ISI at which the earliest-onset of short-latency facilitation was observed for the group was -3.50 ± 0.85ms. The timing at this ISI was considered to represent the fastest TMS descending activity coinciding with the afferent volleys from PNS at the spinal motoneurons. ISI -1ms for SLF and ISI 10.5ms for LLF were determined to be 'standard' ISIs that may elicit maximal or near-maximal facilitation for the group. LLF showed greater variability in the optimal ISI eliciting peak facilitation compared to SLF, which may relate to the more complex and poly-synaptic physiological pathways involved in LLF.Conclusion: Measurement of SLF at a single, standardized ISI may suffice. For measurement of LLF, determining an individual's optimal ISI may provide a more accurate measure. Our findings suggest that evaluating short- and long-latency facilitation of H-reflexes at a range of ISIs may provide a unique opportunity to index the excitability of descending corticofugal projections onto spinal motor neurons.

Disclosures: J. Xu: None. **A. Lopez:** None. **M. Hoque:** None. **M. Borich:** None. **T. Kesar:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.11/OO4

Topic: E.06. Posture and Gait

Support: R01 NS097781

Title: Evidence for separate descending control of clasp-knife inhibition and force feedback in the feline spinal cord

Authors: *E. KAJTAZ[1], M. A. LYLE[2], K. A. CHEFFER[3,4,7,5], L. R. MONTGOMERY[4,3,7], D. R. HOWLAND[4,3,6,7,5], T. NICHOLS[1]
[1]Sch. of Biol. Sci., Georgia Inst. of Technol., Atlanta, GA; [2]Div. of Physical Therapy, Emory Univ., Atlanta, GA; [3]Kentucky Spinal Cord Injury Res. Ctr., Louisville, KY; [4]Dept. of Neurolog. Surgery, [5]Dept. of Anatom. Sci. and Neurobio., [6]Dept. of Bioengineering, Univ. of Louisville, Louisville, KY; [7]Robley Rex VA Med. Ctr., Louisville, KY

Abstract: Spinal cord injury (SCI) can amplify and redistribute intermuscular inhibitory force feedback (iFFB) from Golgi tendon organs and release clasp-knife inhibition (CKI), a powerful inhibition arising from group III and IV muscle receptors. The CKI can be evoked experimentally by transecting the dorsal spinal cord, and the reorganization of iFFB can be evoked by lateral hemisection. Since dorsal and lateral hemisections share disruption of the dorsolateral spinal cord, it is not clear whether CKI and iFFB are regulated by the same supraspinal system. Prior data from our group implicates the vestibulospinal tract, a ventral pathway, in iFFB regulation. To investigate whether inhibitory feedback from these receptor groups are regulated by separate pathways, we sought to determine whether dorsal hemisection alters the organization of iFFB. In the absence of SCI, iFFB between muscles is often bi-directional or evenly balanced and CKI is rarely observed, while following lateral hemisection iFFB is strongly biased toward one member of each muscle pair. Observation of bi-directional iFFB between muscle pairs and presence of CKI following dorsal hemisection would support the hypothesis that iFFB is regulated separately from CKI by descending signals in ventral pathways. We utilized the decerebrate cat and measured the strength and distribution of inhibitory feedback between extensor muscles spanning one or more joints of the feline hind limb. The muscles included members of the quadriceps and triceps surae groups, a long toe flexor, and plantaris. The animals had received either chronic dorsal or lateral hemisections prior to the terminal experiments. Following the decerebration and removal of anesthesia, muscles in pairs, denoted as recipient and donor, were stretched in different combinations and intermuscular inhibition assessed as a decrease in the stretch reflex of the recipient muscle. Intermuscular reflexes due to iFFB were indicated by short-latency, force dependent inhibition, while CKI was indicated by profound and long-lasting inhibition often including autogenic inhibition. The results indicate that iFFB between members of several muscle pairs remained bidirectional following dorsal hemisection, supporting the hypothesis that CKI and iFFB are regulated by distinct descending systems, further distinguishing these two spinal networks. This finding has important clinical implications as presence of either CKI or redistributed iFFB points to the damage to distinct spinal cord columns and can be used as an early diagnostic tool to evaluate the extent and location of the injury. Funding: R01 NS097781

Disclosures: E. Kajtaz: None. **M.A. Lyle:** None. **K.A. Cheffer:** None. **L.R. Montgomery:** None. **D.R. Howland:** None. **T. Nichols:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.12/OO5

Topic: E.06. Posture and Gait

Support: VA RR&D Merit B2316-R

VA RR&D B7165-R
VA RR&D RCS B9249S
NINDS NS097781
NICHD HD32571
NIH 8-P30GM103507
Kentucky Spinal Cord and Head Injury Research Trust

Title: Impact of spinal cord injury on adaptations in stance during down-slope walking

Authors: *L. R. MONTGOMERY[1,2,4], K. A. CHEFFER[1,2,3,4], E. KAJTAZ[5], M. A. LYLE[6], T. NICHOLS[5], D. R. HOWLAND[1,2,3,4]
[1]Dept. of Neurolog. Surgery, [2]Kentucky Spinal Cord Injury Res. Ctr., [3]Anatom. Sci. and Neurobio., Univ. of Louisville, Louisville, KY; [4]Robly Rex Veterans Affairs Med. Ctr., Louisville, KY; [5]Sch. of Biol. Sci., Georgia Inst. of Technol., Atlanta, GA; [6]Div. of Physical Therapy, Emory Univ., Atlanta, GA

Abstract: Features of the step cycle stance phase are finely controlled to ensure stable, efficient weight support during locomotion. Early stance (E2) encompasses the critical period of weight acceptance (yield). During level walking, transition to the second subphase of stance (E3) begins with extension across the hip, knee, ankle. Currently, we are interested in how features of E2 and E3 change with declining walking surfaces, walking speed and following spinal cord injury (SCI). Further, we are interested in understanding how changes in underlying length and force feedback (FFB) systems may contribute to the instability and decreased efficiency of weight support following neurological injury. Given that effective community ambulation involves negotiating different environments at various cadences, understanding these issues may improve rehabilitation outcomes. In the current study, the adult cat, low thoracic, lateral hemisection model is used. Cats are conditioned to step with their hind limbs on a treadmill at various decline angles (0^o to -26^o) at two speeds (0.5 and 0.8 m/s). Angular kinematics are generated and analyzed using a Vicon motion capture system. Our findings indicate that, in the intact cat, with increasing decline slope E2 duration increases, at times lasting throughout stance. The increase in duration of E2 is primarily due to changes at the knee. Further, on the steeper decline(s), a period emerges in which the knee and ankle angular positions remain constant before extension of one or both joints. Amplification of these adaptations is seen at the slower gait speed. Following hemisection, normal adaptations to slope angle during E2 and E3 are disrupted. These disruptions are greater at slower speeds. Impairments in the adaptations to increasing slope are present bilaterally despite the asymmetry of the lesion model. Some features of these impairments in the ipsi- and contra-lesional hind limbs, however are not symmetrical suggesting different combinations of deficit, recovery and compensation across the two hind limbs. How these features change across time, their correlation(s) with underlying changes in length and FFB, and the effect of decline training on recovery are being investigated. This work will help refine our understanding of the E2, E3 subphases during decline walking and the effect of SCI on key features of stance. Supported by Dept of VA, RR&D Merit B2316-R, B7165-R & RCS B9249S, NINDS NS097781, NICHD HD32571, NIH 8-P30GM103507, The Kentucky Spinal

Cord and Head Injury Research Trust, & Rebecca F. Hammond Endowment. Disclaimer - The contents of this presentation do not represent the views of the DVA, NIH or the US government.

Disclosures: L.R. Montgomery: None. **K.A. Cheffer:** None. **E. Kajtaz:** None. **M.A. Lyle:** None. **T. Nichols:** None. **D.R. Howland:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.13/OO6

Topic: E.06. Posture and Gait

Support: Heart of Stroke Foundation
Natural Sciences and Engineering Research Council

Title: Cutaneous reflex modulation in arm muscles during self-triggered and prolonged stimulation

Authors: *Y. SUN, G. PEARCEY, E. ZEHR
Sch. of Exercise Science, Physical and Hlth. Educ., Univ. of Victoria, Victoria, BC, Canada

Abstract: Sensory feedback plays important roles in regulating movement. Some research suggests that cutaneous reflex amplitudes are reduced when the stimulation is self-triggered instead of externally triggered. Corticospinal and spinal excitabilities are altered with different stimulation durations and frequencies. However, the importance of stimulation mode (self or externally triggered) and duration (brief or sustained) is unclear. This study investigated how different combinations of trigger modes and stimulation parameters could affect the modulation of cutaneous pathways to arm muscles. Cutaneous reflexes in the wrist muscle extensor carpi radialis were evoked in neurologically intact young adults with brief (15ms, 300Hz) or sustained (300ms, 50Hz) stimulation trains. Stimulation was applied to the superficial radial nerve at the wrist and triggered by 1) computer; 2) muscle contraction; 3) participant button press. During each condition, wrist extensor muscles were contracted at 10, 25, 35, and 50% of maximal voluntary contraction. Larger cutaneous reflex amplitudes were found with increasing background muscle activities at early and middle latency. Reduced reflex amplitudes were found in the EMG-trigger condition with brief stimulation, but was not seen in the sustained stimulation condition.These results suggest reflex amplitudes following brief stimulation are altered when sensory feedback is enhanced at the onset of muscle contractions. Modulation of cutaneous reflex pathway excitability is specific to the timing when sensory cue was applied. This method can be applied to study sensory regulation of movement performance or facilitate training outcomes.

Disclosures: Y. Sun: None. **G. Pearcey:** None. **E. Zehr:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.14/OO7

Topic: E.06. Posture and Gait

Support: NSERC Discovery Grant

Title: The arms and legs work better when used together: Amplification of rhythmic activity-dependent suppression of soleus Hoffmann reflexes

Authors: *G. E. PEARCEY[1], E. ZEHR[2]
[1]Rehabil. Neurosci. Lab., Univ. of Victoria, Victoria, BC, Canada; [2]Rehab Neurosci. Lab., Victoria, BC, Canada

Abstract: Arm cycling causes suppression of soleus (SOL) Hoffmann (H-) reflex amplitudes that outlasts the activity period. Arm cycling presumably activates propriospinal networks that modulate group Ia presynaptic inhibition. These interlimb pathways are thought to relate to the control of quadrupedal locomotion, allowing for smooth and coordinated movement of the arms and legs. We examined whether the number of active limb pairs affects the amount and duration of activity-dependent plasticity of the SOL H-reflex. On separate days, twelve participants completed 4 randomly ordered 30 minute experimental sessions: 1) quiet sitting (CTRL); 2) arm cycling (ARM); 3) leg cycling (LEG); and, 4) arm and leg cycling (A&L) on an instrumented ergometer. H-reflex and M-wave amplitudes in the SOL were evoked via electrical stimulation of the tibial nerve at the popliteal fossa. M and H-reflex recruitment curves were recorded while the participants sat quietly prior to, 10 and 20 minutes into, immediately after, and at 2.5, 5, 7.5, 10, 15, 20, 25, and 30 minutes after the experimental session. Normalized maximal H-reflexes were unchanged in CTRL but were suppressed by ~30, 45 and 50% for the ARM, LEG and A&L conditions, respectively. Suppression of maximal H-reflexes outlasted activity duration for ARM ($\leq$2.5 mins), LEG ($\leq$5 mins), and A&L ($\geq$30 mins) conditions. The non-linear duration of suppression of reflexes in the A&L condition was greater than the algebraic summation of effects in ARM and LEG. This non-linear summation suggests that using the arms and legs simultaneously—as in normal locomotor synergies—causes amplification of networks responsible for the suppression of soleus H-reflexes. This enhanced activity of spinal networks may have important implications for the implementation of locomotor training for targeted rehabilitation.

Disclosures: G.E. Pearcey: None. **E. Zehr:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.15/OO8

Topic: E.06. Posture and Gait

Support: NSERC Discovery Grant

Title: Neurophysiological and performance changes during long-term Yuishinkai martial arts training: A pilot study

Authors: *A. HARRISON, P. ZEHR, H. MUSTAFA, Y. SUN, G. PEARCEY
Univ. of Victoria, Victoria, BC, Canada

Abstract: Corresponding Author: AMH
Senior Author & Principal Investigator: EPZ
Dynamic postural regulation is a key variable for quality of life and function as we age. Widely available interventions to maintain or enhance integrated function across the lifespan and in the neurologically impaired are needed. Previous research has shown exercise programs to have beneficial effects, yet evidence is lacking in the mind-body exercise interventions. The goal of this research was to advance current findings in a cost-effective therapeutic manner. We investigated the effects of a 5-week mind-body martial arts exercise intervention on postural control, spinal cord excitability and strength. A convenience sample of apparently healthy young adults participated 3 x 1 h per week martial arts sessions lead by an experienced, certified Yuishinkai karate instructor. Using a multiple-baseline control in in pre- and post-assessments, dynamic balance, postural sway, spinal cord excitability (via Hoffmann reflex modulation) and strength were measured. Results showed changes in grip strength, dynamic balance performance and spinal cord excitability suggesting increased postural integration.
It can be anticipated that implementation of a similar karate mind-body exercise program will have a beneficial effect on the overall physical functioning in neurologically compromised individuals.

Disclosures: A. Harrison: None. **P. Zehr:** None. **H. Mustafa:** None. **Y. Sun:** None. **G. Pearcey:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.16/OO9

Topic: E.06. Posture and Gait

Support: The Craig H. Neilsen Foundation, Grant 339705
New York State Department of Health, Spinal Cord Injury Research Program, Contract C32095GG
New York State Department of Health, Spinal Cord Injury Research Program, Contract C32248GG

Title: Transspinal stimulation during treadmill walking alters soleus H-reflex excitability in healthy humans

Authors: *L. M. MURRAY[1], J. LI[2], M. A. ISLAM[3], T. S. PULVERENTI[1], M. KNIKOU[4]
[1]Dept. of Physical Therapy, CUNY Col. of Staten Island, Staten Island, NY; [2]Staten Island Tech. High Sch., Staten Island, NY; [3]Physical Therapy, [4]The Grad. Ctr., City Univ. of New York, Staten Island, NY

Abstract: Non-invasive transspinal stimulation over the thoracolumbar region produces significant modulation of cortical and spinal neural circuits. However, the effects of transspinal stimulation on the phase-dependent modulation of the soleus H-reflex during human walking remain largely unexplored. In this study, we investigated the phase-dependent modulation pattern of the soleus H-reflex following transspinal conditioning stimulation, as well as the phase-dependent modulation pattern of the transspinal evoked potentials (TEPs) during treadmill walking. The soleus H-reflex was conditioned by transspinal stimulation delivered at an individualized negative conditioning-test (C-T) interval that produced reflex facilitation, and at the corresponding positive C-T interval that produced reflex inhibition at rest. During walking, the soleus H-reflex was elicited following posterior tibial nerve stimulation with a 1-ms single pulse at an intensity that the M-waves ranged from 2 to 8 % of the maximal M-wave (Mmax) elicited 60-80 ms after the test reflex stimulus. This protocol was utilized for both unconditioned and conditioned H-reflexes. Soleus TEPs were evoked following cathodal pulsed transspinal stimulation over the thoracolumbar enlargement based on established experimental protocols utilized extensively in our laboratory. Soleus H-reflexes and TEPs were recorded randomly across the step cycle, which was divided equally into 16 bins with bin 1 corresponding to heel contact, and bins 9 and 16 corresponding approximately to stance-to-swing and swing-to-stance transition, respectively. Conditioned and unconditioned H-reflexes and associated M-waves were normalized to the Mmax evoked at each associated bin. TEPs during walking were normalized to the homonymous TEP recorded during standing. The soleus H-reflex was depressed from bins 2

to 9 following positive transspinal conditioning, and facilitated at bin 1 whilst reaching control reflex values at the remaining phases of the step cycle following negative transspinal conditioning. Changes in H-reflex amplitudes occurred with constant M-waves for all conditions. Lastly, the TEPs of distal and proximal limb muscles were modulated in a phase-dependent pattern and linearly with the homologous EMG. We conclude that transspinal stimulation may be utilized as a means to decrease spinal reflex hyper-excitability during walking, as is the case for neurological disorders, and thus promote a physiological gait pattern.

Disclosures: L.M. Murray: None. **J. Li:** None. **M.A. Islam:** None. **T.S. Pulverenti:** None. **M. Knikou:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.17/OO10

Topic: E.06. Posture and Gait

Support: The Craig H. Neilsen Foundation, Grant 339705
New York State Department of Health, Spinal Cord Injury Research Program, Contract C32248GG
New York State Department of Health, Spinal Cord Injury Research Program, Contract C32095GG

Title: Transspinal stimulation affects muscle activation patterns during treadmill walking in healthy humans

Authors: *M. A. ISLAM[1], J. LI[3], T. S. PULVERENTI[4], L. M. MURRAY[4], M. KNIKOU[2]
[1]Physical Therapy, [2]The Grad. Ctr., City Univ. of New York, Staten Island, NY; [3]Staten Island Tech. High Sch., Staten Island, NY; [4]Dept. of Physical Therapy, CUNY Col. of Staten Island, Staten Island, NY

Abstract: Non-invasive transspinal stimulation over the thoracolumbar region produces bilateral transspinal evoked potentials (TEPs) from proximal and distal limb muscles during treadmill walking, which are modulated in a phase-dependent manner. However, the effects of transspinal stimulation on the muscle activation pattern during human walking remain largely unexplored. In this study, we recorded the EMG activity from leg muscles when transspinal stimulation was delivered as a single 1 ms pulse and/or as a pulse train at 30 Hz delivered randomly across the step cycle based on a signal from the foot switches. Each step cycle was divided equally into 16 bins with bin 1 corresponding to heel contact, and bins 9 and 16 corresponding approximately at stance-to-swing and swing-to-stance transition, respectively. We found that the EMG activation patterns from the steps before transspinal stimulation were similar to the homologous EMG

activation patterns recorded after transspinal stimulation. However, the EMGs from the steps during transspinal stimulation indicated different activation patterns. The EMG activation patterns of the ankle extensors shifted from stance to swing phase when stimulation was delivered at bins 5-15, while for ankle flexors these patterns shifted from swing to stance phase when stimulation was delivered at bins 4-16. Importantly, despite this shift, the principle component analysis revealed that bins 1-7 contributed mainly to the ankle extensors EMG activity, and bins 8-11 and 15-2 contributed largely to the ankle flexors EMG activity. We conclude that transspinal stimulation produces complex effects on EMG activation patterns in both ankle extensors and flexors.

Disclosures: M.A. Islam: None. **J. Li:** None. **T.S. Pulverenti:** None. **L.M. Murray:** None. **M. Knikou:** None.

Poster

673. Posture and Gait: Reflexes and Reflex Modulation

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 673.18/OO11

Topic: E.06. Posture and Gait

Support: The Craig H. Neilsen Foundation [Grant 339705]
New York State Department of Health, Spinal Cord Injury Research Program [Contracts C32095GG, C32248GG]

Title: Spinal neural interactions during transspinal and afferent stimulation in humans

Authors: *M. KNIKOU[1], L. M. MURRAY[3], T. S. PULVERENTI[3], M. ISLAM[2]
[1]The Grad. Ctr., [2]Physical Therapy, City Univ. of New York, Staten Island, NY; [3]Dept. of Physical Therapy, CUNY Col. of Staten Island, Staten Island, NY

Abstract: Non-invasive transspinal stimulation may constitute a novel method of neuromodulation and neuroplasticity. However, neural interactions between transspinal evoked potentials (TEPs) and spinal monosynaptic reflexes remain poorly understood. In this study, we established the modulation profile of soleus H-reflexes and TEPs in healthy human subjects, when both stimuli evoked equal in amplitude responses relative to the soleus maximal M-wave. Soleus H-reflexes were evoked by posterior tibial nerve stimulation based on established experimental protocols utilized extensively in our laboratory. Soleus TEPs were evoked by placing two re-usable self-adhesive electrodes (anode), connected to act as one electrode, bilaterally on the iliac crests or parallel from the umbilical line depending on each subject's comfort. A re-usable pre-gelled electrode (cathode) was placed on the thoracolumbar region at T10-L1 under constant pressure throughout the experiment whilst the subject was lying supine. Soleus H-reflexes and soleus TEPs were recorded at conditioning-test (C-T) intervals ranging

from negative to positive 100 ms. A negative C-T interval refers to the interval that transspinal stimulation was delivered after tibial nerve stimulation. The soleus H-reflexes were facilitated at the negative C-T intervals ranging from 16 to 9 ms, and coincided with concomitant depression of soleus TEPs. In contrast, at the negative C-T intervals of 4 and 1 ms, and at the positive C-T intervals of 0 to 100 ms the soleus H-reflex was depressed while soleus TEPs amplitude remained unchanged. Based on these findings, it is apparent that neural interaction of TEPs and monosynaptic Ia excitation of soleus motoneurons are complex in nature, and that changes in excitability depend largely on the timing between the two stimuli. The soleus H-reflex facilitation at negative C-T intervals may be the result of increased depolarization of soleus motoneurons by transspinal stimulation. The soleus H-reflex depression at long C-T intervals suggests the involvement of complex spinal interneuronal circuits following transspinal stimulation. Further research is needed to delineate the specific nature (synaptic vs. non-synaptic and presynaptic vs. postsynaptic) of transspinal stimulation induced reflex actions. Better understanding of the neuronal pathways of action will enable the development of targeted neuromodulation protocols via transspinal stimulation.

Disclosures: M. Knikou: None. **L.M. Murray:** None. **T.S. Pulverenti:** None. **M. Islam:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.01/OO12

Topic: E.08. Respiratory Regulation

Support: National Sanitarium Association Foundation Grant (Richard L. Horner)

Title: Novel zebrafish models to understand respiratory depression and analgesia by opioids and to identify safe opioid pain therapies

Authors: S. ZAIG[1], C. DA SILVEIRA SCARPELLINI[1], X.-Y. WEN[1,3], *G. MONTANDON[2,1]
[2]Dept. of Medicine, Univ. of Toronto, [1]St. Michael's Hosp., Toronto, ON, Canada; [3]Med. & Physiol., Univ. of Toronto, Toronto, ON, Canada

Abstract: Introduction: Opioid drugs are the mainstay of pain management, but their use is limited by their severe side-effects that can be lethal with overdose. Indeed, opioid drugs induce respiratory depression, that can lead to severe hypoxemia and respiratory arrest when opioids are abused. The current antidote naloxone (Narcan) is a life-saving therapy, but its use is limited because it can only be given after the overdose occurs, so it is not a preventive treatment. The main challenge in opioid drug discovery is therefore to develop new opioid therapies with potent analgesia but reduced respiratory depression, so opioids can be safely prescribed. **Objectives:** To accelerate drug discovery, we established phenotype-based approaches using *in vivo* zebrafish

models of respiratory depression and analgesia. Zebrafish is an amenable model to study respiratory depression because its respiratory circuits are similar to mammalian circuits. Also, zebrafish μ-opioid receptors have 70% homology of amino acids with their mammalian counterparts. Our aim was to developed a high-throughput screening platform that combines drug screening and behavioural profiling so new preventive therapies can be identified. **Methods:** To determine respiratory depression, we assessed buccal movements, as an index of respiratory activity, in zebrafish larvae (day post-fertilization 14), and its response to the μ-opioid receptor analgesic fentanyl. We used a video-recording system to assess zebrafishes in multi-well microplate. To assess opioid analgesia, we induced mild pain in zebrafish larvae by submerging it in a solution of acetic acid, or acetic acid/fentanyl, and measuring its subsequent locomotor or swimming response. **Results:** Fentanyl (1 μM) significantly decreased the rate of buccal movements by 84% (baseline 41.7 breath/min, fentanyl 6.71 breath/min, n=3, *P=0.011*), a depression reversed by naloxone (10 μM, 44.3 breath/min). Our preliminary data show that acetic acid (0.01%) strongly increased locomotion, and this response was significantly reduced by fentanyl (1 μM), an analgesic effect blocked by naloxone (10 μM). **Discussion:** Our novel and unique zebrafish models mimicked well the effects of opioid drugs on respiratory activity and nociception observed in mammals. This proof-of-principle study suggests that zebrafish can be used to develop phenotype-based high-throughput drug and gene screening. Using these assays, we will knock-down key-genes involved in opioid inhibition using morpholino oligonucleotides, and test chemical screens to identify preventive therapies to reduce opioid-induced respiratory depression without altering their analgesic properties.

Disclosures: S. Zaig: None. **C. da Silveira Scarpellini:** None. **X. Wen:** None. **G. Montandon:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.02/OO13

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01

Title: AAV-mediated conditional expression of Cyto-111 in primary neuron cultures: Towards understanding idiotypic toxicity and therapeutic efficacy

Authors: *S. WOLFE[1], P. BODNER[1], E. VAZQUEZ-CINTRON[1], K. ICHTCHENKO[2], C. SHOEMAKER[3], M. EISEN[1], P. MCNUTT[1]
[1]USAMRICD, Gunpowder, MD; [2]Sch. of Med., New York Univ., New York, NY; [3]Tufts Univ., Medford, MA

Abstract: Botulinum neurotoxins (BoNTs) are recognized as one of the most deadly toxins to human. Their long-lasting nerve effects combined with a high toxicity profile make them a potentially lethal chemical warfare agent. BoNTs have two domains: a neuron-specific receptor-binding domain called the heavy chain (HC), which is responsible for presynaptic compartment translocation, and a metalloprotease, or light chain (LC), domain that cleaves one or more soluble NSF attachment protein receptor (SNARE) proteins. BoNTs act within nerve terminals to prevent acetylcholine release, resulting in neuromuscular paralysis. Current treatment for BoNT poisoning relies on neutralization of circulatory toxins via passive immunization with antitoxins. However, this approach is ineffective once the toxin has been internalized into peripheral neurons. Patients that do not respond to antitoxin require intensive care, consisting of ventilator support and parenteral nutrition. As a way to combat the toxicity of BoNT/A, we have developed a recombinant derivative of botulinum neurotoxin serotype C (BoNT/C ad) as a molecular vehicle to deliver therapeutic moieties to the neuronal cytosol. BoNT/C ad has been modified to eliminate catalytic activity against neuronal SNARE proteins, putatively rendering it atoxic. By fusing a function-blocking, single-chain antibody to BoNT/C ad, Dr. Ichtchenko (NYU) produced a new molecular entity (called Cyto-111) that delivers a therapeutic moiety directly to the intra-neuronal site of toxic activity. In murine efficacy studies, a single dose of Cyto-111 prevented death in mice intoxicated with 2x LD_{50} BoNT/A at times when antitoxin was completely ineffective. However, in mouse safety studies, we found that Cyto-111 had an inherent toxicity with an estimated median lethality of 2.2 mg/kg. Mice administered this dose developed symptoms similar to botulism, which resolved within 48 h in survivors. Patch clamp recordings from cultured neurons intoxicated with Cyto-111 demonstrated significant decreases in evoked release, suggesting a novel non-proteolytic toxic mechanism. To investigate the mechanism(s) involved in Cyto-111 toxicity, we created a tet-regulated viral construct expressing Cyto-111 and are testing the effects of conditional overexpression on neuronal function in cultured primary neurons. We anticipate these data will identify the novel mechanism of non-proteolytic toxicity of Cyto-111 through whole-cell patch clamp electrophysiology data.

Disclosures: P. Bodner: None. **E. Vazquez-Cintron:** None. **K. Ichtchenko:** None. **C. Shoemaker:** None. **M. Eisen:** None. **P. McNutt:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.04/OO15

Topic: E.08. Respiratory Regulation

Support: Ontario Thoracic Society (G.M.)
Division of Respirology Pettit Block Term Grant (G.M.)
Canadian Institutions of Health Research (R.L.H.)

National Sanitarium Association Innovative Program (R.L.H.)

Title: The regulator of G-protein signaling 4 modulates opioid-induced respiratory depression

Authors: *J. DANAF[1,2], H. LIU[2], R. HORNER[2,3], G. MONTANDON[1,2], C. DA SILVEIRA SCARPALLINI[1], W. WANG[1]
[1]St. Michael's Hosp., Toronto, ON, Canada; [2]Dept. of Medicine, Univ. of Toronto, Toronto, ON, Canada; [3]Dept. of Physiology, Univ. of Toronto, Toronto, ON, Canada

Abstract: **Rationale** Opioid drugs are widely used clinically as analgesics, but present the severe side effect of respiratory depression that can be lethal with overdose. Over 90 Americans die of opioid overdose every day due to respiratory depression. It is therefore critical to better understand the mechanisms regulating opioid-induced respiratory depression to identify new preventive treatments for it. Respiratory depression is due to opioids binding to μ-opioid receptors (MORs) in brainstem respiratory circuits. The preBötzinger Complex (preBötC), a site in the medulla critical for respiratory rhythm, is an important component of respiratory rate depression by opioid drugs (*Montandon et al., 2011, J. Neuroscience*). Binding of opioid drugs to MORs activate intracellular G-proteins and open G-protein-activated inwardly-rectifying potassium (GIRK) channels (*Montandon et al., 2016, Anesthesiology*). Regulators of G-protein signaling (RGS) inhibit GIRK channel activation, but their role in MOR inhibition, especially in the context of respiratory depression, is unknown. Here we aim to identify the molecular mechanisms regulating MOR inhibition of respiratory circuits and the role of RGS4 protein, a common RGS protein found in neurons. **Methods** To determine whether RGS4 is present in the preBötC and whether it is co-expressed with MORs, we used *in situ* hybridization for RGS4 and OPRM1 genes, the genes coding for RGS4 and MORs (RNAscope). To identify the functional role of RGS4, we microperfused RGS4 inhibitors and MOR agonists in the preBötC while recording respiratory muscle activity in anesthetized male Wistar rats. We used the RGS4 inhibitor CCG 50014 (20 μM) in combination with the MOR agonist DAMGO (5 μM) or DAMGO alone. **Results** RGS4 was co-expressed with OPRM1 in the preBötC as well as the nucleus tractus solitarius. RGS4 was also expressed in the facial nucleus, and OPRM1 in the nucleus ambiguus. Microperfusion of DAMGO (5 μM) into the preBötC of anesthetized rats elicited a 24.8±1.2% decrease in respiratory rate (*n=3, P=0.04*). Microperfusion of CCG 50014 (20 μM) and DAMGO (5 μM) potentiated DAMGO inhibition and decreased respiratory rate by 43.5±6.8% (*n=9, P=0.06*), a decrease significantly more pronounced than DAMGO alone (*P=0.04*). **Conclusion** RNA transcripts showed that RGS4 is co-expressed with Oprm1 in the preBötC and other key respiratory circuits, suggesting a role for RGS4 in MOR inhibition. Indeed, inhibition of RGS4 accentuates respiratory inhibition by MOR ligands. Our data suggest that RGS4 plays a functional role in opioid-induced respiratory depression and could potentially constitute a new target to prevent respiratory depression by opioids.

Disclosures: J. Danaf: None. **H. Liu:** None. **R. Horner:** None. **G. Montandon:** None. **C. da Silveira Scarpallini:** None. **W. Wang:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.05/OO16

Topic: E.08. Respiratory Regulation

Support: NIH/NCCAM R01 AT008632
FAPESP #2013/06077-5
FAPESP #2015/06550-8
NIH/NIBIB U01EB021960

Title: Sympathetic overactivity after chronic intermittent hypoxia has different mechanisms in male and female rats

Authors: *W. H. BARNETT[1], G. M. P. R. SOUZA[2], B. H. MACHADO[2], Y. I. MOLKOV[1]
[1]Dept. of Mathematics and Statistics, Georgia State Univ., Atlanta, GA; [2]Dept. of Physiology; Sch. of Med. of Ribeirão Preto, Univ. of São Paulo, Ribeirão Preto, Brazil

Abstract: Untreated sleep apnea may lead to hypertension, which is an indicator of early death. Enhanced respiratory modulation in sympathetic nerve activity (SNA) is thought to mediate hypertension in sleep apnea patients. The mechanisms by which this enhancement occurs are not well understood. Rats subjected to chronic intermittent hypoxia (CIH) are an animal model of obstructive sleep apnea. During CIH conditioning periodic excursions in blood-gas balance repetitively activate peripheral chemoreceptors. Long term exposure evokes plasticity in brainstem neuronal circuitry which appears as changes in respiratory and sympathetic motoneuron output. In male rats, a hallmark of CIH conditioning is the appearance of active expiration during restful breathing. It is thought that late-expiratory activity in the SNA contributes to elevated blood pressure in these animals. Female rats subjected to CIH develop hypertension, but they do not experience a change in the threshold for active expiration. Instead, there is a notable facilitation of early-inspiratory activity in the sympathetic motor output. By what mechanism do female rats respond to CIH conditioning? Previously, we investigated the formation of abdominal activity and SNA in male CIH rats in the context of central chemoreflex activation. In our computational model, we showed that sensitization of the central chemoreceptors to CO_2 was sufficient to lower the threshold for respiration in hypocapnia and lower the threshold for emergence of active expiration to occur during normocapnia. Here, we use our computational model to recapitulate experimental observations of female rats exposed to CIH. From this data, we assimilate (1) the facilitation of early-inspiratory SNA and (2) evidence that inspiratory neurons recorded in the ventral respiratory group decrease firing rate. Via model simulations we generate the hypothesis that there is decrementing inspiratory inhibition on pre-sympathetic rostral ventrolateral medulla (RVLM) neurons in naive animals that is necessary for

SNA pattern formation. Taking into consideration that the caudal VLM (CVLM) is the main source of inhibition to RVLM, we implemented an inhibitory population in CVLM that is modulated by inspiration in the model. In simulation of CIH conditioned female rats, the suppression of this population disinhibits pre-sympathetic neurons in the RVLM which facilitates SNA during early inspiration. These results suggest that male and female rates develop different plastic changes in the medullary respiratory-sympathetic network that both result in enhancement of sympathetic motoneuron output following CIH conditioning.

Disclosures: W.H. Barnett: None. **G.M.P.R. Souza:** None. **B.H. Machado:** None. **Y.I. Molkov:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.06/OO17

Topic: E.08. Respiratory Regulation

Support: CIHR
AIHS
NSERC
CFI
WCHRI

Title: cAMP-dependent modulation of I_h underlies the $P2Y_1$receptor-mediated excitation of the preBötzinger complex inspiratory network *in vitro*

Authors: *Y. ZHANG[1], T. A. JAIB[1], A. V. GOURINE[4], S. KASPAROV[5], T. ALVARES[1], F. D. GREGORY[1,2,3]
[1]Dept. of Physiol., [2]Women & Children's Hlth. Res. Inst., [3]Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada; [4]Dept. of Neuroscience, Physiol. & Pharmacol., Univ. Col. London, London, United Kingdom; [5]Sch. of Physiol. & Pharmacol., Univ. Bristol, Bristol, United Kingdom

Abstract: The ventilatory response to hypoxia comprises an initial, peripheral chemoreceptor-mediated increase in ventilation followed by a centrally-mediated secondary depression that can be life-threatening in premature infants with apnea. Recent evidence suggests that the secondary depression is not just the result of central inhibitory mechanisms but an interaction between inhibitory and excitatory mechanisms. Specifically, ATP appears to be released from astrocytes in the preBötzinger Complex (preBötC, critical site for inspiratory rhythm generation) during hypoxia where it attenuates the secondary depression via a $P2Y_1$ receptor (R)-dependent excitation of inspiratory neurons. Here we apply nerve and whole-cell recording methods to

rhythmic medullary slices (700 µM) from neonatal rat to test the hypothesis that the $P2Y_1R$-mediated excitation of the preBötC network is mediated via cAMP-dependent modulation of the hyperpolarization-activated inward current, I_h, in inspiratory neurons. Local application of MRS2365 ($P2Y_1R$ agonist, 100 µM) evoked, in a subpopulation of inspiratory neurons (~33%), inward currents that reversed between -50 and -60 mV, consistent with activation of I_h. MRS2365 also potentiated the sag current, characteristic of I_h, that was progressively activated with hyperpolarizing voltage pulses from -50 to -110 mV (10 mV increments; 32 ± 6% potentiation measured at -100 mV, n=8). Comparison of I_h activation curves, produced via analysis of tail currents evoked by a series of 10 mV hyperpolarizing steps from -50 mV to -140 mV, in control and MRS2365, revealed a 9.8 mV, MRS2365-induced depolarizing shift in $V_{1/2}$ (V_m at which I_h activated to 50% of maximum, n=6). The MRS2365 inward current and its potentiation of I_h were blocked by local pre-application of ZD 7288 (open channel blocker of I_h, 100 µM). At the network level, pre-application of ZD 7288 at 100 µM (n=6) and 25 µM (n=10) reduced the MRS2365-induced increase in inspiratory-related frequency by 94 ± 3% and 70 ± 12%, respectively. $P2Y_1Rs$ typically operate through activation of the G_q second messenger pathway, whereas I_h is modulated via G_s activation of cAMP. We therefore examined the involvement of cAMP in the $P2Y_1R$ modulation of preBötC neurons and rhythm. 15-min intracellular dialysis of SQ 22536 (adenylyl cyclase inhibitor, 100 µM) via the whole-cell pipette significantly attenuated the MRS2365 currents by 60 ± 4% (n = 9). Similarly, SQ 22536 (100 µM) attenuated the MRS2365-induced frequency increase by 67 ± 8% (n = 8). These data suggest that the $P2Y_1R$-mediated excitation of the preBötC network is produced via a cAMP-dependent modulation of I_h in a subpopulation of inspiratory neurons.

Disclosures: T.A. Jaib: None. **A.V. Gourine:** None. **S. Kasparov:** None. **T. Alvares:** None. **F.D. Gregory:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.07/OO18

Topic: E.08. Respiratory Regulation

Support: DTRA CBM.THRTOX.01.10.RC.021
NIH-NIAID R01 5R01AI093504
ORISE
Cytodel, Inc
Geneva

Title: Intra-neuronal delivery of a single chain antibody as a post-symptomatic treatment of botulism

Authors: *E. VAZQUEZ-CINTRON[1], J. CONNOLLY[2], L. TENEZACA[3], M. EISEN[4], C. ONDECK[5], D. L. NGUYEN[6], P. M. MCNUTT[7], K. ICHTCHENKO[9], M. MANGKHALAKHILI[8]
[1]US Army Med. Res. Inst., APG, MD; [2]The United States Army Med. Res. Inst. of Chem. Def., APG, MD; [3]Cytodel, Inc, New York, NY; [4]Neurosci., USAMRICD, Baltimore, MD; [5]USAMRICD, APG, MD; [6]USAMRICD, Aberdeen Proving Ground, MD; [7]USAMRICD, Fallston, MD; [8]USAMRICD, Abingdon, MD; [9]NYU Sch. of Med., New York, NY

Abstract: Botulinum neurotoxins (BoNTs) are acknowledged as a serious military and civilian mass casualty threat with the potential to rapidly overwhelm medical resources due to their remarkably high potency and easy of production from natural sources. From the seven BoNT serotypes recognized by the CDC (/A - /G), BoNT/A is the most prevalent in human botulism. BoNT/A blocks acetylcholine release by cleaving SNAP-25 in neurons, stalling neuromuscular communication, which results in flaccid muscle paralysis, respiratory failure, and death in the absence of intensive intervention (ventilatory support and intravenous feeding). Presently, there is no treatment to inactive the protease activity of BoNT/A within the neuron to reverse clinical symptoms of muscle paralysis. The only FDA-approved treatment is infusion of antibody-based antitoxins to neutralize BoNT that is circulating in the blood stream by passive immunization. Here, we described a first-in-class treatment based on the targeted intra-cellular delivery of single-domain antibodies (SDA) to the presynaptic compartment of neurons. This technology was used to engineer an antidote treatment (Cyto-111), intended to block the toxin's activity at the site of intoxication (pre-synaptic compartment of neurons) and prevent death when administered after the onset of symptoms. When injected into mice, Cyto-111 traveled to the pre-synaptic compartment of the neuromuscular junction of the diaphragm. In murine efficacy studies, treatment with Cyto-111 prevented death at stages of disease that are completely refractory to antitoxin treatment (standard care treatment). In guinea pig efficacy studies, treatment with Cyto-111 had a 55% statistically significant increase in survival compared to vehicle-treated animals. Currently, we are evaluating the safety and efficacy of Cyto-111 in Rhesus macaques. Collectively, these data show that Cyto-111 successfully reverses clinical symptoms of botulism and prevent mortality following exposure to lethal doses of BoNT/A. Cyto-111 represents a first-in-class, novel therapeutic approach that allows the delivery of single domain antibodies to the presynaptic compartment of neurons.
Disclaimer: The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government. The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense.

Disclosures: E. Vazquez-Cintron: 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.; Cytodel, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cytodel, Inc. **J. Connolly:** None. **L. Tenezaca:** None. **M. Eisen:** None. **C. Ondeck:** None. **D.L. Nguyen:** None. **P.M. McNutt:** None. **K. Ichtchenko:** E. Ownership Interest (stock, stock options,

royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cytodel, Inc. F. Consulting Fees (e.g., advisory boards); Cytodel, Inc. **M. Mangkhalakhili:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.08/PP1

Topic: E.08. Respiratory Regulation

Support: NINDS R01 NS095842
University of Iowa Graduate College Post-Comprehensive Research Fellowship
Neuroscience Training Grant, NIH (T32-NS007421)
Tross Research Fund

Title: Effects of bilateral suprachiasmatic nucleus lesion on circadian rhythms of baseline breathing and hypercapnic ventilatory responses in mice

Authors: *B. S. PURNELL[1], G. F. BUCHANAN[2,1]
[1]Interdisciplinary Grad. Program in Neurosci., [2]Neurol., Univ. of Iowa, Iowa City, IA

Abstract: It is widely agreed that breathing is subject to circadian regulation. Circadian differences in respiratory physiology and responsiveness to hypercapnia are relevant to diseases such as obstructive sleep apnea (OSA) and sudden unexpected death in epilepsy (SUDEP). SUDEP is the leading cause of death in refractory epilepsy and tends to occur at night. The nocturnal occurrence of SUDEP has been attributed to seizures originating from sleep being potentially more dangerous, but circadian variations in seizure occurrence or breathing could play a role. Notably, an endogenous free-running respiratory rhythm has not previously been demonstrated. Also, it is assumed that circadian rhythms in breathing are dependent on the master circadian oscillator in the hypothalamic suprachiasmatic nucleus (SCN), but this has not been shown experimentally. To determine whether breathing is subject to endogenous circadian regulation, the breathing of adult, male, C57BL/6 mice (n = 17) at baseline and in response to 7% CO2 was monitored using whole body plethysmography at 6 different times-of-day (zeitgeber time 2, 6, 10, 14, 18, and 22) while being housed under normal light-dark conditions and at 6 different circadian phases (circadian time 2, 6, 10, 14, 18, and 22) in constant darkness. Mice were housed with running wheels, and the daily running wheel activity was used to assess light entrainment and free-running circadian period. EEG and EMG was recorded concomitant to respiratory monitoring so that sleep state could be determined. Epochs of breathing which occurred during sleep were excluded from this analysis. To determine whether circadian regulation of breathing requires the SCN, this structure was electrolytically (1 mA, 15 s) lesioned bilaterally (n = 11) or a sham surgery was performed (n = 6). After surgical recovery, breathing

was measured at different time points in constant darkness. At baseline, minute ventilation was significantly higher during the active phase in both entrained and free-running conditions. This difference was primarily driven by an increase in respiratory rate, with no change in tidal volume. Furthermore, the respiratory response to CO2 was more robust during the active phase in both conditions. Circadian variations in ventilation and in respiratory responses to CO2 were abolished by SCN lesion. Lesion size and placement were histologically verified post hoc. These results suggest that breathing is under endogenous circadian control via the SCN. Insights into the mechanism of circadian regulation of breathing may lead to targeted interventions which could reduce the morbidity and mortality associated with diseases such as OSA and SUDEP.

Disclosures: B.S. Purnell: None. **G.F. Buchanan:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.09/PP2

Topic: E.08. Respiratory Regulation

Support: NIH R01-NS086088

Title: In-vivo implementation of a neuromorphic controller for ventilatory pacing

Authors: *R. SIU[1], J. J. ABBAS[2], B. K. HILLEN[1], R. JUNG[1]
[1]Biomed. Engin., Florida Intl. Univ., Miami, FL; [2]Sch. of Biol. and Hlth. Systems Engin., Arizona State Univ., Tempe, AZ

Abstract: Ventilation is driven by a complex biofeedback loop that drives pulmonary gas exchange to maintain homeostasis. Trauma or disease in any of the components in this loop can disrupt it and cause ventilatory impairment. Cervical spinal cord injury, for example, may lead to ventilatory paresis or paralysis. Mechanical ventilators have been used as the standard for treatment, but they have risks such as damage to lung tissue and muscle atrophy. Ventilatory pacing systems address these issues by electrically stimulating the diaphragm muscle to cause a contraction of the muscle and thus evoke a breath. Commercially-available pacing systems are all open-loop systems that require lengthy or subjective calibration procedures in a clinical or surgical setting. Any changes to the system during its use requires calibration, which can be inconvenient and costly.
A neuromorphic closed-loop adaptive controller for ventilatory pacing has been developed that can account for biomechanical, physiological, or metabolic change to provide the necessary ventilation. This neuromorphic controller is composed of a pattern generator (PG) that applies a mathematical model of the respiratory central pattern generator to generate a ventilatory pattern based on end-tidal CO_2 input and an adaptive single-layer neural network as the pattern shaper

(PS) that uses measured breath volume to determine the stimulation parameters required to evoke a volumetric profile that matches the pattern generated by the PG.
The PG/PS controller was tested in-vivo in an intact Sprague-Dawley rat. Urethane was used as the anesthetic agent. Bilateral stimulating electrodes were implanted in the diaphragm muscle proximal to the innervation point. A pneumotachometer and a capnograph were used to collect flow and $etCO_2$ values, respectively; flow was integrated to obtain breath volume. After pacing had initiated and adapted to match an initial ventilatory pattern determined by the PG, in order to assess the controller's capabilities, a change in metabolism was mimicked by manually altering the $etCO_2$ input to the controller. A decrease in input to the PG from the initial value of 49 mmHg $etCO_2$ to 48 mmHg $etCO_2$ resulted in a reduction of the weight-matched desired ventilatory profile by 0.15 ml tidal volume and respiratory rate by 11 breaths/min, which the pacing matched after a period of desynchronization lasting 7 cycles. These results show the capability of the controller to modulate both breath volume and respiratory rate in-vivo on a breath-to-breath basis in response to changes in measured $etCO_2$.

Disclosures: R. Siu: None. **J.J. Abbas:** None. **B.K. Hillen:** None. **R. Jung:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.10/PP3

Topic: E.08. Respiratory Regulation

Support: Dept. of Psychology, Illinois State Univ.
School of Biol. Sci., Illinois State Univ.

Title: Effects of serotonin depletion on respiratory and cardiac responses to the 5-HT agonist 8-OH-DPAT and on brain tryptophan hydroxylase immunoreactivity

Authors: J. L. BUTLER[1], N. MICHALAK[2], *B. A. HEIDENREICH[2]
[2]Psychology, [1]Illinois State Univ., Normal, IL

Abstract: Activation of 5-HT1A receptors by systemically administered 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) increases respiratory rate and decreases heart rate. These responses appear to be central in origin, as local application of 8-OH-DPAT to the ventral medulla also produces these effects. However, it is unknown if the 5-HT1A receptors that influence respiratory and cardiac activities are presynaptic autoreceptors or are post-synaptic receptors. This experiment investigated this issue by examining the effects of (±)8-OH-DPAT (0.5-256μg/kg iv) on respiration and heart rates in urethane anesthetized male Sprague-Dawley rats after serotonin depletion with the synthesis inhibitor para-chlorophenylalanine (PCPA; 400 mg/kg sc for 3 days). We then examined tryptophan hydroxylase immunoreactivity in the pons.

Basal respiration rate after treatment with PCPA was 70.5 ± 2.4 breaths/min (n=30), which is significantly slower ($p<.02$) than the breathing rate of 86.8 ± 2.9 breaths/min seen in controls (n=36). 8-OH-DPAT increased breathing rate in 17/27 PCPA-treated rats and 15/22 controls, with no significant difference in either the maximal effect (112-119% of baseline) or the ED50 (20-36μg/kg). Thus, serotonin depletion reduced basal respiration rate without altering the increase in breathing produced by systemic 8-OH-DPAT. Basal heart rate in PCPA-treated rats (5.3 ± 0.1 beats/sec, n=32) did not differ from that in controls (5.0 ± 0.1 beats/sec, n=37). 8-OH-DPAT decreased heart rate in 27/29 PCPA-treated rats and 24/28 controls. The maximal reduction produced by 8-OH-DPAT was significantly greater ($p<.05$) in PCPA-treated rats (76.1 ± 1.6% of baseline), compared to controls (81.6 ± 2.0% of baseline). While serotonin depletion did not alter basal heart rate, the decrease in heart rate produced by 8-OH-DPAT was potentiated, suggesting 5-HT1A receptor supersensitivity. Interestingly, immunostaining for tryptophan hydroxylase in the dorsal raphe nucleus was comparable between control and PCPA-treated rats. While PCPA inactivates tryptophan hydroxylase, thus reducing serotonin levels, the enzyme is still present and immunoreactive within serotonergic neurons. Together, these data indicate that while basal breathing rate may be regulated by tonic serotonergic neuronal activity, postsynaptic 5-HT1A receptors likely mediate the effects of 8-OH-DPAT on respiration and heart rates.

Disclosures: J.L. Butler: None. **N. Michalak:** None. **B.A. Heidenreich:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.11/PP4

Topic: E.08. Respiratory Regulation

Support: 610-5108000-60034952

Title: Leptin regulates breathing by potentiating a background conductance in LepRb-expressing galaninergic neurons in the Nucleus of the Solitary Tract (NTS)

Authors: *J. DO[1], L. FLOREANI[2], G. SEKERKOVA[1], D. R. MCCRIMMON[1], M. MARTINA[1]
[1]Physiology, Feinberg Med. Sch., Northwestern Univ., Chicago, IL; [2]Neurobio., SISSA, Trieste, Italy

Abstract: A remarkable characteristic of the respiratory system is the matching between ventilation and metabolism which is so precise that there is almost no change in arterial blood gases in the presence of different metabolic rates, suggesting that chemoreceptor activation cannot explain the ventilatory response. We speculate the existence of a neural circuit that receives chemosensory information but also receives information related to metabolism. The

caudal nucleus of the solitary tract (NTS) receives dense innervation from sensory afferents of the vagal and glossopharyngeal nerve and there is a noticeable group of cells in the NTS that express the functional long-form leptin receptor (LepRb). Leptin is known to stimulate breathing, and as leptin also increases energy expenditure, the concomitant change in respiration is essential to maintain arterial blood gas homeostasis. Our study has three main goals: 1- to characterize the neurochemical and electrophysiological properties of LepRb-expressing cells in the NTS; 2- to uncover the identity of the ion channel(s) mediating the action of leptin in these different cellular populations; and 3- to identify the properties of fast and slow synaptic transmission of LepRb-expressing NTS neurons that control breathing. To pursue these goals, we combine genetic tagging of leptin receptor expressing neurons, electrophysiological recordings, single cell RT-PCR and in situ hybridization to test the expression of a list of channels and neuropeptides. We found that LepRb-expressing NTS neurons consist of at least two populations based on distinct firing patterns. Type1 cells have burst-like firing patterns whereas type2 cells show delayed spike onset. Leptin depolarizes type1 cells by activating a current mediated by NALCN channels and a major percentage of type1 cells co-express galanin. Together our data suggest that LepRb-expressing NTS neurons form different subpopulations and that the depolarizing action of leptin on galaninergic LepRb cells is at least in part mediated by NALCN channels. To investigate whether galaninergic LepRb-NTS neurons control breathing, we are conducting virus injections into the caudal NTS to map afferents in the ventral respiratory columns.

Disclosures: J. Do: None. **L. Floreani:** None. **G. Sekerkova:** None. **D.R. McCrimmon:** None. **M. Martina:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.12/PP5

Topic: E.08. Respiratory Regulation

Support: NIH Grant R00-DC-012803
NIH Grant R01-DC-016364
NIH Grant T32-NS047987

Title: Automated analysis of breathing using BreathMetrics: A respiratory signal processing toolbox

Authors: *T. J. NOTO
Ward Building 13-270, Northwestern Univ., Chicago, IL

Abstract: Our ability to investigate questions about the neuroscience of respiration and olfaction can only be as good as our ability to link biological events to features of respiratory waveforms.

Human respiratory flow recordings are difficult to analyze because there are inherently noisy, non-stationary, non-sinusoidal, and imbued with a multitude of meaningful features that vary across individuals. With no tool for automatically extracting the full set of features hidden in raw respiratory recordings, researchers must build time-intensive, custom analysis protocols that often require hand-labeling each respiratory event in a recording. This methodology limits comparison across studies as well as the range and precision of possible insights that can be gained about the brain's respiratory and olfactory processing. Here we present BreathMetrics: an open-source respiratory signal processing toolbox that automatically calculates the full set of features embedded in airflow recordings (including sniff onsets), calculates statistical summaries of these features, and visualizes them. Here we show that BreathMetrics passes a rigorous validation process by evaluating BreathMetrics' feature estimation accuracy using several techniques on recordings from human subjects, mice, and simulations. BreathMetrics' feature estimates were more accurate and revealed stronger odor-evoked theta power in electrophysiological recordings of human olfactory cortex compared to other techniques, these features resemble those that were hand-labeled, and feature estimations had 95% confidence intervals on the order of single milliseconds. Using this tool, we were able to glean new insights about how respiratory waveforms change when individuals perform an emotional task in basal and induced anxious states. In this way, we show that our algorithm accurately and thoroughly analyzes respiratory waveforms, allowing researchers to address novel questions about how respiration relates to body, brain, and behavior.

Disclosures: T.J. Noto: None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.13/PP6

Topic: E.08. Respiratory Regulation

Support: NSERC 435843
CIHR RES0032721

Title: Etonogestrel: Effect on ventilation in adult female rats

Authors: *J. SAINI[1,2], L. DEHOOG[2], S. PAGLIARDINI[3]
[1]Neurosci. and Mental Hlth. institute, [2]Univ. of Alberta, Edmonton, AB, Canada; [3]Physiol., Univ. Of Alberta, Edmonton, AB, Canada

Abstract: It is well known that progesterone acts both centrally and peripherally as a respiratory stimulant, as women who are in the luteal phase of their menstrual cycle or during pregnancy experience periods of hyperventilation, and post-menopausal women display an increased

frequency of sleep disordered breathing compared to pre-menopausal women.
Congenital central hypoventilation syndrome (CCHS) is a disorder caused by a genetic mutation of the transcription factor paired-like homeobox 2b (PHOX2B), which is essential for neural development of several classes of neurons in the brainstem. CCHS is associated with the inability to maintain proper ventilation and blood gas levels during sleep. There is no effective cure for the disease and the only option for treatment is mechanical ventilation or diaphragm pacing. Respiratory stimulants have proven ineffective, with the exception of a recent report that indicated a 2-3 fold increase in the ventilatory response to hypercapnia in female CCHS patients with the onset of desogestrel, a potent progestin into their daily regimen.
In this study we hypothesized that etonogestrel (ETO; the active metabolite of desogestrel) stimulates progesterone receptor expressing neurons to increase ventilation. Adult female rats were instrumented with implants to chronically deliver ETO (or sham rats) over a four-week period. An additional group of rats was also treated with 17β estradiol (E2) to increase progesterone receptor expression in presence of ETO or sham rats. Rats were then tested weekly in whole-body plethysmographs to determine changes in respiratory parameters (frequency, tidal volume, and minute ventilation) during baseline conditions (normoxia) and respiratory challenges (hypercapnia and hypoxia). At the end of the experiment, response to hypoxia and hypercapnia was also tested under isofluorane anesthesia.
Our results indicate that ETO does not affect the hypercapnic or hypoxic ventilatory response in freely behaving healthy female rats. However, ETO or E2 induce potentiation in the second phase of the hypoxic ventilatory response under isofluorane anesthesia.

Disclosures: J. Saini: None. **L. DeHoog:** None. **S. Pagliardini:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); MERCK.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.14/PP7

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01 AG044615

Title: Mitochondrial density and morphology in phrenic motor neurons is size-dependent

Authors: *S. RANA[1], M. J. FOGARTY[2], C. B. MANTILLA[3], G. C. SIECK[2]
[1]Neurobio. of Dis., [2]Physiol. & Biomed. Engin., [3]Anesthesiol., Mayo Clin., Rochester, MN

Abstract: Neuromotor control of diaphragm motor units is dependent on the orderly recruitment of phrenic motor neurons (PhMNs) in a size-dependent manner. Type S and FR motor units comprise smaller, more easily recruited PhMNs that innervate fatigue resistant, lower force-

producing type I and type IIa muscle fibers. Type FInt and FF motor units, comprise larger, rarely recruited PhMNs innervating the more fatigable, higher force-producing type IIx and/or IIb muscle fibers. The activity and energy demand upon PhMNs of type S and FR motor units is greater than that of PhMNs from type FInt and FF units, due to the high duty cycle (~35%) of ventilation. Accordingly, activity of type FInt and FF motor units is largely the domain of higher force behaviors, performed over much shorter durations, including expulsive/straining maneuvers such as coughing, sneezing, defecation and parturition. The energy demand in both PhMNs and diaphragm muscle fibers is met by mitochondria. To preserve homeostasis, mitochondrial functions are regulated by dynamic, continuous cycles of fusion and fragmentation. We hypothesized that mitochondrial density and mitochondrial fusion will be greater in smaller PhMNs, due to their more frequent activation during ventilation. In six adult (6-month old) Fischer 344 rats, PhMNs were retrogradely labeled by intrapleural injection of Alexa488-conjugated CTB. Three days later, cervical transdural infusion of MitoTracker Red was performed every 10 min for 1.5 h under anesthesia. Spinal cord tissue was collected following transcardial perfusion with 4% paraformaldehyde, sectioned longitudinally at 70 µm, and mounted onto slides. Two-channel sequential confocal z-stack (0.50 µm step size) mosaics of PhMNs and mitochondria were acquired using a 60x oil immersion objective and analyzed using Nikon Elements software. The surface areas of PhMNs were measured and divided into tertiles. The lower tertile of PhMNs (comprising type S and FR motor units) had greater mitochondrial volume densities, greater mitochondrial aspect ratios and form factors and greater mean individual mitochondrial volumes than upper tertile PhMNs (comprising type FInt and FF motor units). We further characterized the differences in mRNA expression of mitochondrial dynamics associated proteins (Mfn2 and Drp1) in large vs. small PhMNs using fluorescent in-situ hybridization techniques. Our results suggest that PhMNs of type S and FR motor units have increased mitochondrial density, supporting their high energy demand to sustain ventilation. Their increased mitochondrial fusion may underlie their resilience to PhMN loss in aging and disease.

Disclosures: S. Rana: None. **M.J. Fogarty:** None. **C.B. Mantilla:** None. **G.C. Sieck:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.15/PP8

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01 HL96750

Title: Glutamatergic synaptic input to phrenic motor neurons depends on motor neuron size

Authors: *G. C. SIECK[1], S. RANA[2], W.-Z. ZHAN[3], C. B. MANTILLA[4]
[1]Physiol. & Biomed. Engin., [2]Neurobio. of Dis., [4]Anesthesiol., [3]Mayo Clin., Rochester, MN

Abstract: Excitatory glutamatergic (Glu) synaptic input responsible for inspiratory drive to phrenic motor neurons (PhMNs) emanates primarily from the ipsilateral ventrolateral medulla. This excitatory input is disrupted by unilateral C2 hemisection (C2SH), resulting in cessation of inspiratory-related diaphragm muscle (DIAm) activity. In previous studies we found that while inspiratory-related DIAm EMG activity disappears immediately after C2SH, DIAm activity during higher force behaviors persists. These higher levels of DIAm force are necessary to generate greater intra-abdominal pressures during expulsive airway clearance and straining behaviors. In a model of PhMN (DIAm motor unit) recruitment, we hypothesized that smaller PhMNs innervating more fatigue resistant DIAm motor units are recruited to accomplish ventilatory behaviors, whereas larger PhMNs innervating more fatigable motor units are recruited to accomplish more forceful expulsive/straining behaviors. These two general classes of DIAm motor behaviors are likely to have different synaptic drive to PhMNs. Accordingly, we hypothesize that C2SH primarily disrupts Glu synaptic inputs to smaller PhMNs, whereas Glu synaptic inputs to larger PhMNs are preserved after C2SH. To address this hypothesis, we examined changes in Glu presynaptic input onto retrogradely labeled PhMNs using immunohistochemistry for VGLUT1 and VGLUT2. We found that following C2SH (by 7 days), there was substantial reduction in Glu synaptic input to smaller PhMNs. In contrast, Glu synaptic input to larger PhMNs was relatively unaffected. These results are consistent with a more pronounced impact of C2SH on smaller PhMNs (fatigue resistant DIAm motor units), which are responsible for lower force, ventilatory behaviors of the DIAm. In contrast, the preservation of Glu synaptic input at larger PhMNs (more fatigable DIAm motor units) after C2SH is consistent with the preservation of higher force behaviors after C2SH. These results indicate that the source of Glu synaptic input to PhMNs varies depending on motor neuron size and reflects different functional control -perhaps separate central pattern generator and premotor circuits. For smaller PhMNs, the central pattern generator for respiration is located in the pre-Botzinger complex and premotor neurons in the ventrolateral medulla, sending predominantly ipsilateral projections via the dorsolateral funiculus. C2SH disrupts this Glu input. For larger PhMNs, the central pattern generator for expulsive/straining behaviors and the premotor neurons mediating these behaviors appear to reside below the C2 level, since C2SH does not eliminate Glu input.

Disclosures: G.C. Sieck: None. **S. Rana:** None. **W. Zhan:** None. **C.B. Mantilla:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.16/PP9

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01 HL96750

Title: Cervical spinal hemisection induced changes in phrenic motor neuron TrkB mRNA expression depend on motor neuron size

Authors: *C. B. MANTILLA[1], S. RANA[2], W.-Z. ZHAN[2], G. C. SIECK[2]
[1]Anesthesiol., [2]Physiol. & BME, Mayo Clin., Rochester, MN

Abstract: Among patients with spinal cord injury (SCI), more than 50% involve the cervical spinal cord, with many cases resulting in diaphragm muscle (DIAm) paralysis and impaired ventilation. Importantly, most SCIs are incomplete with sparing of descending excitatory inputs to phrenic motor neurons (PhMNs). Unilateral C2 hemisection (C2SH) is an animal model of incomplete SCI widely used to examine neuroplasticity in the neuromotor control of breathing following injury. In recent studies, we found that the amplitude of ventilatory-related DIAm activity (generally accomplished by recruitment of smaller PhMNs) is reduced after C2SH. Gradual recovery of rhythmic ventilatory-related DIAm activity ipsilateral to injury is evident over time, and is enhanced by BDNF signaling through its high-affinity TrkB receptor in PhMNs, reflecting neuroplasticity. In contrast, DIAm EMG activity during higher force, non-ventilatory behaviors (generally accomplished by recruitment of larger PhMNs) is only minimally impaired. The mechanisms underlying the observed spontaneous recovery remain poorly understood, particularly in light of potential cell specific effects (e.g., across PhMNs of differing size). Thus, we hypothesized that there are size dependent differences in TrkB expression at PhMNs that underlie neuroplasticity after C2SH. To address this hypothesis, TrkB.FL mRNA expression in retrogradely-labeled PhMNs was measured using RNAscope in situ hybridization (ACDBio) up to 21 days post-C2SH in adult male rats. We found that immediately following C2SH (by 3 days), there was absence of ipsilateral DIAm EMG activity during eupnea. TrkB.FL mRNA expression, primarily in smaller PhMNs, was reduced by 3 days post-C2SH. In contrast, TrkB.FL mRNA expression in larger PhMNs was relatively unaffected. By 21 days post-C2SH, 50% of rats displayed recovery of ipsilateral DIAm EMG activity during eupnea and there was a marked increase in TrkB.FL mRNA expression, predominantly in smaller PhMNs. Ipsilateral DIAm EMG activity during sigh (~40% of maximal DIAm activity) was not impacted at any time post-C2SH. These results support an important role for TrkB signaling at PhMNs in the spontaneous recovery of ipsilateral DIAm EMG activity after C2SH and suggest fundamental differences between small and large PhMNs in the mechanisms underlying neuroplasticity and recovery.

Disclosures: C.B. Mantilla: None. **S. Rana:** None. **W. Zhan:** None. **G.C. Sieck:** None.

Poster

674. Motor Control and Modulation of Respiration

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 674.17/PP10

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01-AG044615

Title: Diaphragm neuromuscular transmission failure in aged rats

Authors: *M. J. FOGARTY[1], G. C. SIECK[2], C. B. MANTILLA[3]
[1]Dept. of Physiol. & Biomed. Engin., [2]Physiol. & Biomed. Engin., [3]Anesthesiol., Mayo Clin., Rochester, MN

Abstract: In the aging Fischer 344 (F344) rat, phrenic motor neuron loss and diaphragm muscle weakness and atrophy (sarcopenia) are present by 24-months. Type FInt and FF motor units are particularly vulnerable, with larger MNs more susceptible to age-associated loss and type IIx and/or IIb muscle fibers in old rats having marked reductions in cross-sectional area. Neuromuscular junctions of type FInt and FF motor units are fragmented in old F344 rats. The likelihood of neuromuscular transmission failure is frequency-dependent with type FInt and FF motor units more likely to display neuromuscular transmission failure. Thus, we hypothesized that neuromuscular transmission failure would be evident in older diaphragm muscle preparations, particularly at the higher stimulation frequencies. We stimulated diaphragm muscle-phrenic nerve preparations of adult Fisher 344 male and female rats using supramaximal trains of 330 ms duration (33% duty cycle) at 10, 40 and 75 Hz via the nerve or directly at the muscle. Direct nerve-evoked train stimulations occurred every second for 2 min while indirect muscle stimulations were superimposed every 15 s. Effective neuromuscular transmission and neuromuscular transmission failure was compared between 6-and 24-months of age. Muscle strips were weighed and absolute measures of muscle specific force (normalized to cross-sectional area) and relative force measures were assessed. Effective neuromuscular transmission (initial nerve-evoked contractions compared to initial muscle stimulations) at 40 and 75 Hz was reduced by ~35% in old rats. Continuous stimulation for 2 mins led to neuromuscular transmission failure at 10, 40 and 75 Hz. However, only during 40 and 75 Hz stimulations were we able to detect a further likelihood of failures (increased by 20%) in old compared to young F344 rats. There were no observable age-associated differences at 10 Hz stimulations in F344 rats. The negligible difference in 10 Hz stimulations is consistent with the relative resilience of type S and FR motor units whereas failure at the higher frequencies likely reflects susceptibility of type FInt and FF motor units. These data suggest are consistent with motor unit type-specific neuromuscular impairments contributing to sarcopenia in old rats.

Disclosures: M.J. Fogarty: None. **G.C. Sieck:** None. **C.B. Mantilla:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.01/PP11

Topic: E.09. Motor Neurons and Muscle

Support: JSPS KAKENHI Grant Number JP23890130
Smoking Research Foundation

Title: Optineurin inhibits C2C12 myogenesis but is not associated with TWEAK-related muscle atrophy

Authors: *Y. NAGANO[1], M. ARAKI[1], K. ISHIKAWA[1], T. SHISHIDO[1], T. KURASHIGE[3], T. TAKAHASHI[1], H. KAWAKAMI[2], M. MATSUMOTO[4], H. MARUYAMA[1]
[2]Epidemiology, [1]Hiroshima Univ., Hiroshima, Japan; [3]Neurol., NHO Kure Med. Ctr., Kure, Japan; [4]Sakai City Med. Ctr., Sakai, Japan

Abstract: Mutations in optineurin (*OPTN*) have been identified in a small proportion (<1%) of sporadic and familial amyotrophic lateral sclerosis (ALS) cases. Previous reports have shown that OPTN functions as an autophagy receptor and a negative regulator of nuclear factor kappa B (NF-κB), however the exact role of OPTN in the pathogenesis of ALS remains unclear. To further examine the role of OPTN, we examined whether OPTN is involved in muscle homeostasis *in vitro*. To investigate the molecular role of OPTN in muscle atrophy, we used cultured C2C12 myotubes treated with tumor necrosis factor-like inducer of apoptosis (TWEAK) as an *in vitro* model of muscle atrophy. TWEAK treatment induced muscle atrophy and increased the mRNA levels of muscle ring-finger 1 (MuRF1), which plays an important role in the muscle atrophy process. However, the expression levels of OPTN protein and mRNA did not change significantly. C2C12 myoblasts were transfected with siRNA to knock down the expression of OPTN, differentiated, and then treated with TWEAK. OPTN knockdown had no effect on the process of muscle atrophy in this model. On the other hand, we found that myogenic differentiation was affected by OPTN. Immunoblotting analysis showed that OPTN protein levels gradually decreased during C2C12 differentiation. Furthermore, OPTN knockdown promoted C2C12 differentiation, accompanied by stable expression of myogenic factor 5 (Myf5). These findings suggested that although OPTN was not involved in TWEAK-induced muscle atrophy, OPTN could be a negative regulator of myogenic differentiation.

Disclosures: Y. Nagano: None. **M. Araki:** None. **K. Ishikawa:** None. **T. Shishido:** None. **T. Kurashige:** None. **T. Takahashi:** None. **H. Kawakami:** None. **M. Matsumoto:** None. **H. Maruyama:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.02/PP12

Topic: E.09. Motor Neurons and Muscle

Title: Effect of age on axonal regeneration following peripheral nerve injury: Assessment of myelin content by magnetic resonance imaging (MRI) and post-mortem analysis

Authors: *E. GIORGETTI[1], M. OBRECHT[2], M. PANESAR[2], M. RONCO[2], C. LAMBERT[2], N. ACCART[2], M. NASH[2], M. BIDINOSTI[2], N. BECKMANN[2]
[1]MSD-PN, [2]Novartis Inst. For Biomed. Res., Basel, Switzerland

Abstract: Myelin content can be an important indicator of nerve health and disruption of myelination is associated with several peripheral nerve pathologies, e.g. Charcot-Marie-Tooth Disease. Although extensive investigation has been conducted on axonal pathology in peripheral neuropathies, there is limited research on how nerve health and myelination deteriorates with aging and to which extent this affects regeneration following injury. Here we present a comprehensive analysis of the myelination status in young and old rodents, and following peripheral nerve injury, by longitudinal non-invasive Magnetic Resonance Imaging (MRI) and post-mortem histological assessment. In particular, we examined the potential of Magnetization Transfer Ratio (MTR) as a rapid readout to assess demyelination in two commonly used rodent models of acute nerve injury: sciatic nerve crush and lysolecithin-induced demyelination. Sciatic nerve MTR was reduced in old (18 months) compared to young (9 weeks) mice at baseline (-4.1%). For both groups, MTR declined (-16.5% in young, -11.7% in old animals) one week after nerve crush. Full recovery was observed after six weeks; however, the rate of MTR recovery was faster for young mice. An increased nerve signal intensity was also observed after the crush, suggesting inflammation and/or axonal injury. Changes in nerve MTR were accompanied by a reduction in calf muscle volume (-10.8% in young, -27.4% in old mice), that was still present at week six post-crush. Moreover, an increased T2 relaxation time was observed in the calf muscle one week after the crush in segments distal to the site of injury.
These MRI signal changes correlated with histological and gene expression analysis of post-mortem specimens. In particular, myelin content decreased in the sciatic nerve one week after nerve crush and fully recovered at six weeks in young mice. Parallel macrophage infiltration was also observed in the nerve, consistent with an inflammatory process elicited by the crush. Analogous results were obtained for topical lysolecithin administration to the sciatic nerve in rats. A reduction by 15% in nerve MTR was observed in both young (8 weeks) and old (10 months) rats one week after lysolecithin (0.1 mg). Three weeks following lysolecithin, the MTR had not yet returned to baseline levels, but the rate of recovery was faster in young rats.

Overall, our results underline age differences in recovery following peripheral nerve injury and indicate the usefulness of non-invasive imaging and histological analysis to investigate these models of demyelination in rodents, especially in the context of pharmacological studies.

Disclosures: E. Giorgetti: None. **M. Obrecht:** None. **M. Panesar:** None. **M. Ronco:** None. **C. Lambert:** None. **N. Accart:** None. **M. Nash:** None. **M. Bidinosti:** None. **N. Beckmann:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.03/DP08/PP13

Topic: E.09. Motor Neurons and Muscle

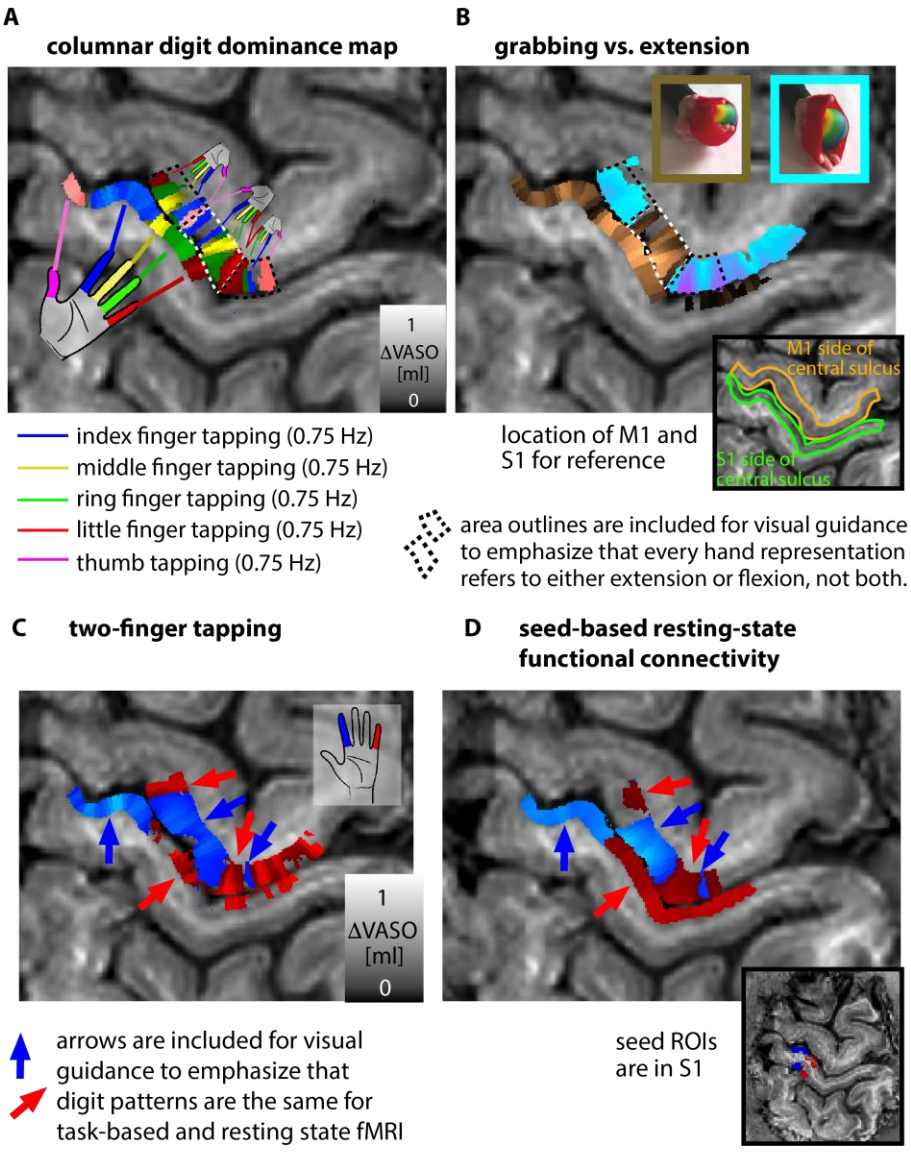
Title: Unique functional digit representation in human motor cortex across columns and layers

Authors: *L. HUBER[1], E. FINN[2], D. GLEN[3], R. REYNOLDS[3], B. POSER[5], P. BANDETTINI[4]
[1]NIMH/LBC/SFIM, Natl. Inst. of Hlth. Office of Intramural, Bethesda, MD; [2]NIMH, Bethesda, DC; [3]NIH, Bethesda, DC; [4]NIH, Bethesda, MD; [5]MBIC, Maastricht, Netherlands

Abstract: The sensorimotor system consists of multiple brain areas, incl. M1 and S1. The neural connections between sensorimotor areas follows pathways that are uniquely distributed across cortical layers and columns. Recently, we found that the analysis of laminar resting-state fMRI fluctuations in M1 are indicative of afferent vs. efferent connectivity in M1 [Huber, Neuron(96), 2017]. In this study, we seek to characterize both the columnar and laminar topology of body-part representations across M1 and S1 using blood-volume-sensitive fMRI at ultra-high spatial resolutions. N=4 participants underwent up to seven 2h fMRI sessions (8h-14h scan time per participant) using resting-state and a variety of movement tasks. The fMRI resolution was 0.78x0.78 (in-plane) with 3D-EPI [Poser, NeiroImage(51), 2010] VASO.
Sensory areas depict a single clear digit organization, as expected. In the hand knob of M1, however, we unexpectedly observe multiple digit representations (Fig. A). Each individual hand representation matches a cortical patch that is differently activated during movements of grabbing vs. extension (Fig. A-B). The same patterns of fine-scale digit representations can be detected both during explicit movement and at rest (Fig. C-D). We find that digit representations in S1 are 3-4 times larger than in M1. Upper layers (II/III) have a higher columnar digit specificity than deeper layers (Vb/VI). While all participants' data revealed at least two hand representations, their topological size and shape was highly variable across individuals.
We conclude that the topology of digit representations in M1 is very complex, and that body-parts within-vertebra representations are not as linearly organized as across-vertebra. This work suggests that advanced high-resolution fMRI can reveal fine scale organizations in M1 that could

only be investigated in animal models so far.

Acknowledgements:
* Esther Kuehn & Sean Marrett (inspiring discussions).
* Dimo Ivanov (sequence parts).
* Andrew Hall & Kenny Chung (scan support)
* NIMH Intramural Research Program.



Disclosures: L. Huber: None. **E. Finn:** None. **D. Glen:** None. **R. Reynolds:** None. **B. Poser:** None. **P. Bandettini:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.04/PP14

Topic: E.09. Motor Neurons and Muscle

Title: Neuroanatomical and functional substrates associated with a single muscle representation

Authors: *A. M. ALBISHI, B. FISHER, J. KUTCH
USC, Los Angeles, CA

Abstract: Background: A muscle can be recruited volitionally as a prime mover or automatically as a postural stabilizer. Any given muscle receives command signals from its representation in both primary motor cortex (M1) and supplementary motor area (SMA). Our goal is to determine if the SMA and M1 representations of an individual muscle that is used both volitionally and automatically (e.g. trunk muscles) are contained in different brain networks, such that one network would be focused on volitional and the other more focused on automatic signaling.
Purpose: To map brain networks including M1 and SMA representations of trunk and hand muscles and determine if trunk muscles are contained in differential brain networks compared to the hand.
Methods: Transcranial magnetic stimulation and task-based functional magnetic resonance imaging (fMRI) were used to map 3-dimensional coordinates (regions-of-interest, ROI) for the SMA and M1 representations of a trunk (external oblique, EO) and hand muscle (first dorsal interosseous, FDI). These ROI were used in a whole-brain functional connectivity analysis utilizing resting-state fMRI (rs-fMRI). For each muscle, the whole-brain functional connectivity map of SMA was compared to M1.
Results: Basal ganglia and cerebellum are more connected to SMA while primary somatosensory and parietal cortex are more connected to M1 for both muscles. Slight differences in lateralization were observed in FDI compared to EO.
Conclusion: Our results suggest the possibility that brain networks underlying more automatic muscle control may extend equally well to distal muscle given that the basic features of differential connectivity of SMA and M1 appeared to be muscle-independent.

Disclosures: A.M. Albishi: None. **B. Fisher:** None. **J. Kutch:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.05/PP15

Topic: E.09. Motor Neurons and Muscle

Support: China Scholarship Council

Title: Evidence of neuromuscular junction remodelling during periods of prolonged muscle inactivity in amphibians

Authors: *D. GE[1], P. G. NOAKES[3], N. A. LAVIDIS[2]
[1]Sch. of biomedical sciences, [2]The Univ. of Queensland, Brisbane, Australia; [3]Univ. of Queensland, Brisbane, Australia

Abstract: At mammalian neuromuscular junctions (NMJs), prolonged inactivity leads to severe degeneration, however amphibian NMJs do not show such severe degeneration even though they can remain inactive for many years of drought imposed inactivity. We have previously reported on the extent of functional inhibition in neurotransmission imposed during the dry season, along with the possible involvement of dynorphin-A. In the present study, we compared NMJ morphology of *Bufo marinus* obtained from the wild during the wet (January to April) and dry (August to November) southern hemisphere seasons. Iliofarbularis muscles were isolated, and prepared for immuno-staining with anti-SV2, a monoclonal antibody that labels synaptic vesicle glycoprotein SV2. These muscles were also stained for the location of post-synaptic acetylcholine receptors (AChRs) using Alexa555 conjugated α-bungarotoxin. Confocal microscopy and 3D reconstruction were then used to examine and compare the pre- and post-synaptic morphology of *Bufo marinus* NMJs from the dry (inactive) and wet (active) seasons. During the dry season, NMJs with large nerve terminals revealed a greater number of branches and increased fragmentation, while medium nerve terminals had fewer branches, when compared to NMJs from the wet season. Further, we observed a lower pre- and post-synaptic apposition (i.e. SV2-AChR overlap) at large NMJs during the dry season, compared to the wet season. Together these observations show that during periods of relative NMJ inactivity (dry season), there exists some NMJ remodelling.

Disclosures: D. Ge: None. **P.G. Noakes:** None. **N.A. Lavidis:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.06/PP16

Topic: E.09. Motor Neurons and Muscle

Support: Ministry of Science, ICT and Future Planning of Korea (18-BT-01)

Title: Modeling the action potential-driven force production in fast skeletal muscles

Authors: *H. KIM[1], T. G. SANDERCOCK[2], C. HECKMAN[2]
[1]Daegu Gyeongbuk Inst. of Sci. & Technol., Daegu, Korea, Republic of; [2]Dept. of Physiol., Northwestern Univ., Chicago, IL

Abstract: The goal of this study is to develop a physiologically realistic model that reflects nonlinear input-output properties of fast muscles over a wide range of physiologically relevant input conditions for stimulation rate and muscle length. To achieve this goal, we adapted our recently developed muscle-tendon model for the cat soleus muscle based on the NEURON platform, which allows direct interactions with simulations of neural circuits. Our target muscle was the cat medial gastrocnemius muscle, which is primarily fast twitch. The differences in muscle activation dynamics between the model and real fast muscle were first identified and characterized under the same rate and length protocols used for soleus. Then, the mechanisms that generated these differences were mathematically formulated and incorporated into the modeling framework. The main differences between the simulation and experimental data were found for unfused contractions, during which the force gradually declined over time. By compensating this sag phenomenon by modulating the dynamics of cross-bridge formation, the extended muscle model could accurately replicate the force production of fast muscles over a full physiological range of muscle length and stimulation rate during isometric and isokinetic contractions. The modeling framework developed in NEURON platform for this study may be useful not only for investigation of neuromusclar interactions but also for development of electrical stimulation treatments and neuroprosthetic devices for movement disorders.

Disclosures: H. Kim: None. **T.G. Sandercock:** None. **C. Heckman:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.07/PP17

Topic: E.09. Motor Neurons and Muscle

Title: Role of fez1 in motor neuron function and associated locomotion function

Authors: *Z. WANG[1], V. J. T. KOK[2], J. J. E. CHUA[2], K. LIM[1,2]
[1]Natl. Neurosci. Inst., Singapore, Singapore; [2]Physiol., Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Neurons, unlike other cells, have elongated processes that require complex intracellular transport machinery to maintain optimal function. It is therefore unsurprising that disruption of this process has been implicated in defective neuronal development and neurodegeneration. Studies have found that loss of FEZ1, an important adaptor for motor protein Kinesin-1, results in perturbed transportation of synaptic vesicles and proteins, and synapse loss. Nevertheless, how FEZ1 mediated transport affects synaptic function remains unclear. Therefore, this project seeks to investigate the effect of loss of FEZ1 function on synaptic morphology and associated behavioural phenotypes. Using *Drosophila* as a model organism, we demonstrated that the loss of UNC-76, the sole *Drosophila* homolog of FEZ1, results in a significant loss of synaptic boutons that is accompanied by locomotion deficits and increased mortality. Importantly, the effect of *unc-76* knockdown on locomotion appears to manifest specifically in motor neurons, indicating that the FEZ1 has a potential role in the maintenance of normal motor neuronal function. Taken together, these results suggest that loss of FEZ1 disturbs the normal formation and/or maintenance of synapses, resulting in behavioural phenotypes and affecting mortality of the organism.

Disclosures: Z. Wang: None. **V.J.T. Kok:** None. **J.J.E. Chua:** None. **K. Lim:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.08/PP18

Topic: E.09. Motor Neurons and Muscle

Support: ERC-2014-CoG-646923_DBSModel

Title: An integrated, mathematical model of excitation-contraction coupling and calcium-activated mitochondrial metabolism in skeletal muscle fibers

Authors: *S. SENNEFF, M. LOWERY
Electrical & Electronic Engin., Univ. Col. Dublin, Dublin, Ireland

Abstract: Mitochondrial abnormalities have been demonstrated in neurodegenerative disorders such as Parkinson's disease, Huntington's disease, and Amyotrophic lateral sclerosis. In addition to changes within the nervous system, experimental studies in skeletal muscle have quantified changes in mitochondrial activity suggested to impact excitation-contraction coupling (ECC), the signalling cascade controlling muscle contraction and relaxation. These include reductions in electron transport chain activity, mitochondrial ATP synthesis, and depolarization-evoked calcium release, linked to elevated mitochondrial ROS production.
Several mechanisms have been proposed to address the cause and effect of these changes within muscle, but testing each hypothesis experimentally is difficult. Integrated computational models of ECC and mitochondrial metabolism could provide a valuable means of exploring effects of these changes on both mitochondrial function and muscle force.
A mathematical model of ECC and calcium-activated mitochondrial metabolism was developed for fast and slow twitch skeletal muscle. A compartmental modelling approach was used where the fiber was split into equally sized 100 μm compartments, each containing a transverse-tubular system modelled as a radial cable. Stimulation at the center of the fiber elicited a bidirectional propagating action potential, initiating ECC and metabolism within each compartment. Changes in transmembrane potential were solved with the cable equation.
Model simulations were performed at a range of stimulation frequencies and temperatures for three case studies: a 25% reduction in depolarization-evoked calcium release, a 25% reduction in the rate of mitochondrial ATP synthesis, and a 50% reduction in electron transport chain activity, in accordance with experimentally observed values. A sensitivity analysis will be performed to determine how, and to what extent, components of the ECC pathway and mitochondrial metabolism are compromised by these changes, with a focus on alterations in muscle force production and mitochondrial membrane potential.
Computational modelling of skeletal muscle activation can be used to explore the effects of neurodegenerative diseases on muscle output. Three case studies were simulated to assess changes in tetanic force production as well as mitochondrial membrane potential, which has been demonstrated to play an important role in apoptosis. Further studies will be done to better understand the effects of mitochondrial abnormalities on skeletal muscle to support pre-existing, or suggest new, testable experimental hypotheses.

Disclosures: S. Senneff: None. **M. Lowery:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.09/PP19

Topic: E.09. Motor Neurons and Muscle

Title: *In vivo* expression of a designer ubiquitinase delays muscle paralysis and accelerates muscle recovery following botulinum toxin A intoxication

Authors: *B. M. WINNER[1], E. VASQUES-CINTRON[1], C. PHUNG[1], A. BRADFORD[2], C. ONDECK[1], P. BODNER[1], P. MCNUTT[1]
[1]USAMRICD, Aberdeen Proving Ground, MD; [2]Univ. of New Hampshire, Durham, NH

Abstract: Botulinum neurotoxins (BoNTs) cleave neuronal SNARE proteins, blocking synaptic transmission. Recent studies indicate that directed ubiquitination of the BoNT/A catalytic light chain using a recombinant E3 ligase can promote ubiquitination and degradation by the ubiquitin proteasome system. To further evaluate the therapeutic utility of directed ubiquitination, we designed transgenic mice expressing a bifunctional designer ubiquitinase consisting of a LC/A function-blocking VHH camelid antibody fused to an F-box protein E3 ligase under the control of the thy1.1 promoter. The transgene was robustly expressed in brain, spinal cord, and diaphragmatic neurons. To characterize effects of transgene expression on intoxication, we evaluated diaphragmatic function ex vivo using isometric twitch contraction following administration of BoNT/A. Diaphragms from wild-type (WT) mice were fully paralyzed within approximately 90 min after intoxication, whereas diaphragms from transgenic mice were paralyzed significantly later at 120 min after BoNT/A intoxication. In pilot dose-response studies, WT and transgenic mice were administered 1-5 LD_{50} doses of BoNT/A in gastrocnemius muscle. All WT mice in the two highest dose groups died within 5 days, whereas no transgenic mice died at any dose. The digit abduction score (DAS) assay, a sensitive index of gastrocnemius muscle paralysis, was further used to evaluate recovery of muscle function. WT mice recovered muscle function after 45 days, whereas recovery of muscle function in transgenic mice occurred within just 3 days. These studies demonstrate that in vivo expression of designer ubiquitinases represents a novel, therapeutically viable strategy to promote recovery from paralysis after BoNT intoxication.

Disclosures: B.M. Winner: None. **E. Vasques-Cintron:** None. **C. Phung:** None. **A. Bradford:** None. **C. Ondeck:** None. **P. Bodner:** None. **P. McNutt:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.10/PP20

Topic: E.09. Motor Neurons and Muscle

Support: New York State Department of Health Spinal Cord Injury Research Board (Contract # C32097GG)
Department of Veterans Affairs Merit Award

Title: Spinal electromagnetic stimulation results in frequency dependent depression with healthy adults

Authors: *S. A. SISTO[1], H. A. PETROSYAN[2], C. ZOU[3], C. LEONE[4], A. TESFA[5], M. FAHMY[5], M. ZAIDI[6], V. L. ARVANIAN[7]
[1]Univ. at Buffalo, Buffalo, NY; [2]Neurobio. and Behavior, [4]Physical Therapy, [3]Stony Brook Univ., Stony Brook, NY; [5]Northport Veterans Affairs Med. Ctr., Northport, NY; [6]SUNY Stony Brook Sch. of Med., Stony Brook, NY; [7]Res. Services, Norhtport VAMC, Northport, NY

Abstract: The H-reflex is recognized as an important neurophysiological tool to evaluate the sensitivity of spino-muscular circuitry. Studies have found that electro-magnetic stimulation on spinal segmental levels (SEMS) can result in an altered threshold intensity and the index of frequency-dependent depression (FDD) of H-reflex. Eight non-injured participants were tested in an IRB approved study at Stony Brook University and the Northport Veterans Affairs Medical Center, 4 from each Center were examined using the FDD index. A protocol was designed to study H-reflex by using tibial nerve electrical stimulation pre- and post- 30 minutes of SEMS on L5/S1 spinal levels with 60-70% coil intensity at 0.2Hz. FDD was measured at the intensity which evoked 30-50% of H-max at 0.2, 1.0 and 2.0 Hz frequencies over 3 sessions for each participant. Data for 11 sessions (n=19 legs) exhibited decreased threshold intensity after the SEMS specifically the FDD was 15% and 7% at 1.0 Hz and 2.0 Hz, respectively. The pre-post data included 4 sessions where the post- H-reflex had an average of 17% less depression at 1.0 Hz and 8% less depression at 2.0 Hz; and in 2 sessions 1 leg exhibited an increase of H-reflex threshold intensity after SEMS. These results provide preliminary normative data to which FDD, when measured in pathology such as spinal cord injury, could be compared.

Disclosures: S.A. Sisto: None. **H.A. Petrosyan:** None. **C. Zou:** None. **C. Leone:** None. **A. Tesfa:** None. **M. Fahmy:** None. **M. Zaidi:** None. **V.L. Arvanian:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.11/PP21

Topic: E.09. Motor Neurons and Muscle

Support: R01-AG044615
R01-HL96750
Australian National Health & Medical Research Council CJ Martin Early Career Fellowship

Title: Neuromuscular transmission failure in an animal model of early onset spasticity

Authors: *J. E. BRANDENBURG[1], M. J. FOGARTY[2], G. C. SIECK[3]
[1]Dept. of Physical Med. and Rehabil., [2]Dept. of Physiol. & Biomed. Engin., [3]Physiol. & Biomed. Engin., Mayo Clin., Rochester, MN

Abstract: Pre- and post-synaptic glycine (Gly) mutations are associated with changes in central synapses (motor neuron (MN)) and peripheral synapses (i.e. neuromuscular junctions (NMJ)). Adult mice lacking Gly receptor (s*pa* [B6.Cg-*Glrb*^{spa}/J]) display marked symptoms of early onset spasticity. In *spa* mice, we have shown that MN pruning is increased, such that fewer MNs are present. With fewer MNs, axonal branching to individual muscle fibers may be increased to maintain innervation (increased innervation ratio), which may also contribute to greater neuromuscular transmission failure (NMTF) due to branch point failure. However, it is not known if *spa* mice have greater NMTF. In humans with early onset spasticity, such as cerebral palsy, death is most commonly due to respiratory disorders. One potential contributor to respiratory disorders may be greater difficulty with respiratory control due to increased NMTF. Thus, we hypothesize that *spa* mice will have greater diaphragm muscle (DIAm) NMTF and muscle fatigue when compared to wild-type (WT) mice. *Ex vivo* diaphragm-phrenic nerve preparations were stimulated with trains of 330 ms duration. Each train had supramaximal amplitude pulses of 40 Hz acting on nerve or muscle. Direct nerve-evoked train stimulations occurred every second for 2 mins. Indirect muscle stimulations was superimposed every 15 s and effective neuromuscular transmission and NMTF compared between *spa* and wild-type mice. The DIAm strip was stimulated across a range of frequencies (from 5 to 100 Hz) in 1 s duration trains with rest periods of 2 min between each frequency to assess the maximal tetanic force. Muscle strips were weighed and absolute measures of muscle specific force (normalized to DIAm cross-sectional areas) and relative measures were assessed. Continuous indirect muscle stimulation (40 Hz) of 330 ms pulses for 2 min was used to assess fatigue in DIAm strips. Effective neuromuscular transmission (initial nerve-evoked contractions compared to initial

muscle stimulations) was 10% less in *spa* mice compared to WT mice (P=0.038) with *spa* mice having greater NMTF than WT mice (P<0.001) over the 2 min duration of stimulation. At the end of stimulation, *spa* mice had a 40% greater NMTF than WT mice (P<0.001). With regard to muscle, s*pa* mice had a 26% reduction in maximal muscle tetanic force (P<0.002) with a 33% increase in muscle fatigue index (P<0.001) as compared to WT mice. Thus *spa* mice have greater DIAm NMTF, reduction in overall DIAm force, and increased muscle fatigue. Currently, we are determining the functional implications of these findings on DIAm force (i.e. transdiaphragmatic pressure (Pdi)) and respiratory function (i.e. plethysmography).

Disclosures: J.E. Brandenburg: None. **M.J. Fogarty:** None. **G.C. Sieck:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.12/PP22

Topic: E.09. Motor Neurons and Muscle

Title: Determination of cellular and molecular mechanisms of 1,1'-methylenebis{4-[(hydroxyimino)methyl]pyridinium} (MMB4) toxicity on rabbit neuromuscular junctions

Authors: *K. PAGARIGAN, J. MACHAMER, B. WINNER, A. BRADFORD, C. PHUNG, C. ONDECK, P. MCNUTT
Res., USAMRICD, Gunpowder, MD

Abstract: The acute toxicity of organophosphorus (OP) compounds is primarily a result of acetylcholinesterase (AChE) inhibition in the central and peripheral nervous systems. Severe OP poisoning causes convulsion, respiratory collapse, and death. Current treatment for OP poisoning includes the administration of the antimuscarinic drug atropine, the anticonvulsive drug benzodiazepam and the oxime pyridine-2-aldoximechloride (2-PAM) to reactivate AChE. However, 2-PAM is only modestly effective against a limited range of OP nerve agents and is toxic near effective concentrations, and therefore an improved oxime with rapid systemic distribution and lower toxicity is critically needed. 1,1′-methylenebis{4-[(hydroxyimino)methyl]pyridinium} (MMB4) is a leading candidate for next-generation nerve agent treatment and is more effective at reactivating AChE than is 2-PAM. Although MMB4 appears clinically nontoxic at effective concentrations in rodents, MMB4 depresses respiratory function in rabbits, causing death at doses exceeding 200 mg/kg. To determine the mechanisms of MMB4 toxicity, we first evaluated concentration-dependent effects of MMB4 on rabbit diaphragm function by measuring ex vivo nerve-elicited isometric twitch, subtetanic, and tetanic contraction strength in New Zealand white female rabbits. Preliminary results indicate a progressive use-dependent inhibition of muscle contraction strength by MMB4, which causes the

complete loss of diaphragmatic function at high concentrations. To determine the molecular mechanisms of MMB4-induced diaphragmatic collapse, we performed ex vivo diaphragm endplate recordings prior to and following perfusion of MMB4. As concentrations of MMB4 increased, endplate potential (EPP) and miniature EPP (mEPP) amplitudes were reduced, while quantal content was unaffected. Additionally at higher concentrations of MMB4, halfwidths of mEPPs and EPPs were increased. These results demonstrate that MMB4 has a multifactorial effect on cholinergic synaptic transmission in rabbits that collectively impairs diaphragmatic function. Future work will focus on the effects of MMB4 in rats to determine the basis for differential toxicity between rabbits and rodents.

Disclosures: K. Pagarigan: None. **J. Machamer:** None. **B. Winner:** None. **A. Bradford:** None. **C. Phung:** None. **C. Ondeck:** None. **P. McNutt:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.13/QQ1

Topic: E.09. Motor Neurons and Muscle

Support: Grant R-719-000-023-112

Title: Fine motor control of a peripheral nerve injured arm achieved through an implantable muscle stimulator

Authors: *T. M. SIBINDI[1], G. G. L. GAMMAD[1], L. ONG[1], I. DEWANY[2], C. W. C. LIM[1], S.-C. YEN[1], C. D. LIBEDINSKY[1]
[1]Natl. Univ. of Singapore, Singapore, Singapore; [2]Paris Descartes Univ., Paris, France

Abstract: ABSTRACT
OBJECTIVES
Central and peripheral nervous system injuries can result in loss of limb movements and the fine motor control of said limbs. To address this problem, we utilized functional electrical stimulation (FES) of peripheral muscles and nerves in the arm of non-human primates (NHPs). Here, we describe the properties of FES in NHPs to restore fine motor control (via an implantable muscle stimulator) required for self-feeding.
APPROACH
Muscle mapping using multiple electrodes were implanted at specific sites for the NHP thumb (flexor pollicis brevis) and the four digits (flexor digitorum superficialis) in healthy animals, as well as animals with peripheral nerve damage. The baseline parameters (50Hz, 4mA, 200μs, 200NoP) allowing the longest sustained contractions were established with healthy innervated

NHPs.
MAIN RESULTS
We were successfully able to generate individual finger movements and hand grasps, using subject-specific FES parameters. We found the denervated NHP arm to be less excitable than a healthy arm as the denervated arm required greater current intensities to elicit a visible contraction of the digits. Overall, denervated NHPs were able to grasp and hold objects of varying weights, ranging from 19.3g to 102.4g. Additionally, to reduce muscle fatigue, which is a major limiting factor of FES, we developed a closed-loop system integrating a force sensor. This allowed us to achieve an adaptive control over the muscle stimulation by modulating FES parameters (frequency and current intensity) to the gripping force of the denervated NHP arm. Using this feedback-controlled electrical stimulation, the denervated NHPs were able to hold the weights for a longer amount of time.
SIGNIFICANCE
We present here the stimulation properties that can lead to sustained grasping of everyday objects, such as a spoon or mug for self-feeding, whilst minimizing muscle fatigue. We endeavour to be able to control fine hand movements used in activities of daily living.

Disclosures: T.M. Sibindi: None. **G.G.L. Gammad:** None. **L. Ong:** None. **I. Dewany:** None. **C.W.C. Lim:** None. **S. Yen:** None. **C.D. Libedinsky:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.14/QQ2

Topic: E.09. Motor Neurons and Muscle

Support: Brown Neuroscience Graduate Program
NIH U01NS064295

Title: Evidence for MuSK-mediated BMP signaling at the neuromuscular junction

Authors: *L. A. FISH[1], D. JAIME[2], A. YILMAZ[3], L. A. MADIGAN[2], J. R. FALLON[1]
[1]Neurosci., [2]Mol. Biology, Cell Biol. & Biochem., Brown Univ., Providence, RI; [3]The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: The stability of the neuromuscular junction (NMJ) is critical for proper motor function and is a target for treating neuromuscular disorders. However, the mechanisms by which the NMJ matures and is maintained remain largely unknown. Muscle-specific kinase (MuSK) is a receptor tyrosine kinase with a well-established role in the agrin-LRP4 pathway mediating NMJ formation and stability (Wu et al., 2010). Recent work from our laboratory shows that MuSK, in

a manner not requiring its tyrosine kinase activity, is also a BMP co-receptor. MuSK binds directly to BMPs, via its Ig3 domain, as well as the BMP receptors ALK3 and ALK6. MuSK shapes BMP stimulated transcriptional output in myogenic cells, notably regulating genes important for NMJ formation including MuSK itself, Dok7 and Wnt11 (Yilmaz et al., 2016). Here, we explore MuSK's role as a BMP co-receptor in regulating NMJ structure. To selectively manipulate MuSK-BMP binding we used CRISPR/Cas9 genome editing to create a mouse line in which the MuSK Ig3 domain is constitutively deleted ('Delta-Ig3-MuSK'). Structural analysis indicates that the levels of synaptic MuSK in Delta-Ig3-MuSK animals are comparable to littermate controls but that the NMJs are abnormal. Confocal analysis revealed that the postsynaptic apparatus in Delta-Ig3-MuSK mice is significantly more segmented compared to wild-type littermates (n=70 sternomastoid NMJs of each genotype from 6 Delta-Ig3-MuSK and 3 wild-type 3-month old animals; Mann-Whitney U-test for difference in segment count, $p<0.0001$). Such fragmentation often indicates impaired NMJ maturation or stabilization (Amenta et al., 2012). Preliminary ultrastructural analysis indicates that the junctional folds in Delta-Ig3-MuSK mice are overall shallower and disorganized compared to wild-type. Additional characterization is in progress. Together, these results suggest that MuSK-BMP signaling plays a role in NMJ organization and stability.

Disclosures: L.A. Fish: None. **D. Jaime:** None. **A. Yilmaz:** None. **L.A. Madigan:** None. **J.R. Fallon:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.15/QQ3

Topic: E.09. Motor Neurons and Muscle

Support: the Institute for Translational Medicine and Therapeutics of the Perelman School of Medicine and the School of Veterinary Medicine at the University of Pennsylvania
the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR001878

Title: Antigen-specific immunotherapy of myasthenia gravis in domestic dogs - a pilot study

Authors: *J. LUO, O. A. GARDEN
Sch. of Vet. Med., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Myasthenia gravis (MG) and its animal model, experimental autoimmune myasthenia gravis (EAMG), are caused by antibody-mediated autoimmune responses to acetylcholine receptors (AChRs) of skeletal muscles that cause complement-mediated destruction of the

AChRs and impairment of neuromuscular transmission, resulting in weakness and fatigability. The specificities of pathological autoantibodies and pathological mechanisms in EAMG and MG are similar. All of the pathological autoantibodies are directed at the extracellular domain of the AChR, especially the main immunogenic region (MIR). We have devised a specific immunosuppressive therapy for EAMG in rats using bacterially-expressed cytoplasmic domains of human AChR subunits in a therapeutic vaccine that prevents the development of chronic EAMG and rapidly suppresses ongoing EAMG. The therapy diverts autoantibody specificities away from pathological extracellular epitopes like the MIR, towards pathological irrelevant cytoplasmic epitopes. This therapy is safe, potent, robust, long-lasting, and avoids the side effects of nonspecific immunosuppressive drugs, which are the mainstay of treatment in human patients. We now translate our rat studies into a spontaneous canine model that recapitulates the human disease in clinical presentation, diagnostic testing, treatments, and immunopathology. We evaluated the safety of the canine-specific vaccine in healthy colony dogs. We are currently investigating the safety and potential efficacy (phase 1/2) of the canine-specific vaccine in a small cohort of client-owned dogs with seropositive generalized MG, serving as a pilot study for a subsequent clinical trial. Evaluation of our therapy in client-owned dogs will provide a better understanding of the likely outcome in human patients, providing a proof-of-principle that will inform and accelerate human clinical trials.

Disclosures: J. Luo: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A patent has been filed on specific immunosuppressive therapy of MG with AChR cytoplasmic domains.. **O.A. Garden:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.16/QQ4

Topic: E.09. Motor Neurons and Muscle

Support: NSF Grant CBET-0939511

Title: Functional outcomes of crosstalk between neural networks and engineered muscle tissues in a novel microfabricated three-dimensional co-culture platform

Authors: *A. PASSARO[1,2], O. AYDIN[4], M. ELHEBEARY[4], G. J. PAGAN-DIAZ[5], A. FAN[4], S. NUETHONG[4], R. BASHIR[5], T. A. SAIF[4], S. STICE[1,3]
[1]Regenerative Biosci. Ctr., [2]Div. of Neuroscience, Biomed. and Hlth. Sci. Inst., [3]Dept. of Animal and Dairy Sci., Univ. of Georgia, Athens, GA; [4]Dept. of Mechanical Sci. and Engin., [5]Dept. of Bioengineering, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Neuromuscular dysfunction is associated with many disorders, such as amyotrophic lateral sclerosis (ALS) and myasthenia gravis. During development, it is well-known that there is substantial crosstalk between neurons and muscle fibers required for proper development and function; however, many of the factors and mechanisms that mediate this crosstalk, as well as corresponding functional outcomes, have yet to be identified. A major reason for the relative lack of exploration into crosstalk mechanisms the lack of physiologically relevant neuromuscular junction (NMJ) models. Much of what is known about NMJs has been contributed from *in vivo* models, but these models tend to be expensive and too complex to examine things at a molecular level, while current *in vitro* models tend to lack sufficient three-dimensionality, compartmentalization, and/or functional endpoints. Here, we present a novel microfabricated culture platform that allows for compartmentalized three-dimensional co-culture of neural and muscle cells. Using this platform to culture optogenetically active embryonic stem cell-derived neurospheres and engineered muscle tissues, we observed preferential neurite outgrowth toward muscle tissues and ultimately innervation and the formation of optogenetically active NMJs. After innervation, the muscle tissues exhibited increased spontaneous and stimulated activity, as measured by both force and contraction frequency, presumably due to spontaneous neural activity. To examine this neural activity in more detail, we dissociated the same neurospheres and seeded them on microelectrode arrays (MEAs), allowing us to analyze neural network activity and development over time. While the cells spontaneously increase firing rate over time, treatment with muscle-conditioned medium significantly increased network activity and accelerated network development and maturation, as measured by network bursting and synchrony metrics. Taken together, the biased neurite outgrowth toward muscle, enhanced muscle contractility in the presence of neurons, and enhanced neural network activity and development in the presence of muscle-conditioned medium suggests that there is substantial reciprocal crosstalk between neural and muscle cells, resulting in significant functional outcomes. In addition, the platform developed here serves as a physiologically relevant method to analyze crosstalk and specific mechanisms underlying NMJ development, both in healthy and disease states. Differences in neuron-muscle crosstalk are likely to be implicated in various neuromuscular disorders and may provide therapeutic targets for future treatments.

Disclosures: A. Passaro: None. **O. Aydin:** None. **M. Elhebeary:** None. **G.J. Pagan-Diaz:** None. **A. Fan:** None. **S. Nuethong:** None. **R. Bashir:** None. **T.A. Saif:** None. **S. Stice:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.17/QQ5

Topic: E.09. Motor Neurons and Muscle

Support: The Swank Family Foundation
The AACPDM – Pedal with Pete Award
Nemours Foundation

Title: Altered muscle satellite cell distribution and phenotype in patients with spastic cerebral palsy

Authors: *S. K. YEAGER[1,2], K. G. ROBINSON[2], E. L. CROWGEY[2], R. E. AKINS[2]
[1]Wilmington, DE; [2]Biomed. Res., Nemours Alfred I duPont Hosp. for Children, Wilmington, DE

Abstract: Spastic cerebral palsy (CP) represents ~80% of CP cases and is characterized by muscle stiffness and contracture with disrupted movement, posture, and gait. Previous research indicates that muscles in individuals with CP have altered fiber type distributions, satellite cell (SC) function, extracellular matrix composition, gene expression profiles, and neuromuscular junction (NMJ) microanatomy. It has been suggested that these disruptions in CP muscle may be inter-related and associated with muscle pathology, but additional research is needed. The current study evaluated SC distribution in tissue, SC function in culture, RNA-Seq profiles, and NMJ organization in spastic CP.
Subjects with CP and controls were enrolled in an IRB approved study. Muscle biopsies were collected for quantitative immunofluorescense (IF) analysis and for SC isolation. We used the tissue location of cells and staining with the cell surface marker NCAM1 (neural cell adhesion molecule) and the transcription factor Pax7 to identify SCs. To evaluate the distribution of SCs, muscle sections were evaluated for the presence of these markers. Data evaluating NMJ organization were derived from IF co-localization of acetylcholine esterase, nicotinic acetylcholine receptor (nAChR), and laminin β2 and correlated with the SC data. SC cell lines isolated from patients with CP (n=6) and controls (n=6) were cultured under proliferation conditions until reaching 60-75% confluence and then switched to differentiation medium for 24 hours. RNA was collected and analyzed by RNASeq.
Results indicated that subjects with CP had fewer SCs overall. CP subjects had a greater proportion of NCAM1-positive / Pax7-negative cells occupying SC niches compared to controls (CP = 0.18 ± 0.001, Ctrl = 0.08 ± 0.0006; $p<0.01$). Among controls, there was a negative correlation between the proportion of NCAM1-positive / Pax7-negative SCs and total nAChR staining (CC=0.997, $p<0.01$); this correlation was not seen in patients with CP. Cultured NCAM-positive/Pax7-positive SCs exhibited diagnosis-related differences in proliferation. Preliminary RNAseq analysis revealed significant differences in the patterns of gene expression in the cohorts. In particular, cultured SCs from patients with CP had significantly altered RNA patterns related to cell growth, cell motility, matrix remodeling, cell differentiation, and NMJ maintenance. Further analysis will elucidate specific relationships between altered SC gene expression, SC phenotype, matrix deposition, neuromotor synapse dysmorphism, and muscle function in CP.

Disclosures: S.K. Yeager: None. **K.G. Robinson:** None. **E.L. Crowgey:** None. **R.E. Akins:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.18/QQ6

Topic: E.09. Motor Neurons and Muscle

Support: NSF STC CBET 0939511 (EBICS)
NSF DGE 1735252 (NRT UtB)

Title: Toward developing biorobots that walk

Authors: *C. KAUFMAN[1], S. C. LIU[1], G. NASERI[1], R. BASHIR[2], M. GILLETTE[3]
[1]Neurosci. Program, [2]Bioengineering, [3]Cell and Developmental Biol., Univ. of Illinois, Urbana-Champaign, Urbana, IL

Abstract: A biorobot is a hybrid machine that combines abiotic and biological components for a wide variety of possible functions. These may include the ability to sense their environment, process signals, and produce force. Recent work in the field of biorobotics has focused on developing a musculoskeletal biological machine that can produce motion in response to controllable external signaling. Here, we report the development of a muscle-cell actuator on a 3D-printed hydrogel skeleton under explicit neuronal control such that this multi-cellular system is able to locomote through its environment by harnessing the emergent properties of vertebrate nervous systems. The use of an intact spinal cord as a neuronal source provides the system with a degree of autonomy that will be critical for many future applications of this technology. Bioengineered soft robots might be used to test disease models, create a "peripheral nervous system-on-a-chip" device for drug safety and efficacy testing, and eventually forward-engineer life forms.

Disclosures: C. Kaufman: None. **S.C. Liu:** None. **G. Naseri:** None. **R. Bashir:** None. **M. Gillette:** None.

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Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.19/QQ7

Topic: E.09. Motor Neurons and Muscle

Support: PAPIIT-UNAM IA203617 (FC)
PRODEP No. 511-6/17-8609 to MACR
Cuerpos Académicos BUAP CA-288

Title: Estrogens influence differentially on myofiber CSA of the pubococcygeus and iliococcygeus muscles in female rats

Authors: *M. D. CARRASCO RUIZ[1,2], E. CUEVAS ROMERO[1], P. PACHECO[3], C. CORTES[4], J. R. EGUIBAR[4], A. HANDALL[4], M. MARTINEZ GOMEZ[5], F. CASTELAN[6]
[1]Univ. Autonoma De Tlaxcala, Tlaxcala, Mexico; [2]Inst. de Investigaciones Biomedicas, Univ. Autonoma de Mexico, Mexico, Mexico; [3]Inst. de Investigaciones Biomédicas, Univ. Nacional Autonoma de México, Xalapa, Mexico; [4]B. Univ. Autonoma de Puebla, Puebla, Mexico; [5]Inst. de Investigaciones Biomedicas, Univ. Autonoma de Mexico, Mexico, Mexico, Mexico; [6]Inst. de Investigaciones Biomedicas, Univ. Autonoma de Mexico, Mexico, Mexico, Mexico

Abstract: Pelvic floor muscles (PFM), such as pubocoocygeus (Pcm) and iliococcygeus (Icm), assist importantly in micturition. Several clinical and basic studies support that some PFM are estrogen sensitive, which explains the prescription of estrogen-based therapies as treatment for women suffering stress urinary incontinence (IUS). Findings from our workgroup, gathered in female rabbits and rats, however, suggest PFM can respond differently to changes in circulating and local estrogen levels. In order to determine whether this presumptive estrogenic sensitivity can be extended to the myofiber cross-sectional area **(**CSA). We used Wistar female rats 1) at proestrus (P) and metaestrus (M) stages of the estrous cycle, 2) sham surgery or 3) ovariectomized (OVX) rats implanted with empty capsules or estradiol benzoate filled capsules; an additional OVX+EB group was administered with a blocker of aromatase activity (1,4,6-Androstatriene-3,17-dione, ATD) was done to approach the contribution of local estrogens. Hematoxilyn-eosin stained transverse sections of the Pcm and Icm were used to measure the myofiber CSA. Results showed an increase in the CSA for the Pcm, but not for the Icm at proestrus. Furthermore, ovariectomy increased the CSA for the Pcm, which was reversed by the EB; the treatment with ATD exacerbated the effect of OVX. No alterations were observed for the Icm. Our results support our hypothesis regarding PFM respond differentially to estrogens in female rats.

Disclosures: M.D. Carrasco Ruiz: None. **E. Cuevas romero:** None. **P. Pacheco:** None. **C. Cortes:** None. **J.R. Eguibar:** None. **A. Handall:** None. **M. Martinez gomez:** None. **F. Castelan:** None.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.20/QQ8

Topic: E.09. Motor Neurons and Muscle

Title: Human IPSC-derived motor neurons: Coculture with skeletal myoblasts and investigating TDP-43 mutations

Authors: B. F. FREITAS[1], L. K. FONG[2], J. LIU[1], B. MELINE[1], C. CHAVEZ[1], *T. FEASTER[4], C. MCMAHON[1], D. MANN[1], W. WANG[1], J. ARJOMAND[3], U. SCHMIDT[5], E. JONES[1]
[1]FUJIFILM Cell. Dynamics, Inc, Madison, WI; [2]Genea Biocells US Inc., La Jolla, CA; [3]Genea Biocells US Inc., San Diego, CA; [4]FUJIFILM Cell. Dynamics, Madison, WI; [5]Genea Biocells Us Inc., San Diego, CA

Abstract: The ability to produce motor neurons from induced pluripotent stem cells (iPSCs) provides the means to model several neuromuscular disorders using human cells. It is now possible to explore human-specific drug screening platforms with prospective treatment possibilities using iPS-derived motor neurons for disorders lacking therapeutic options such as amyotrophic lateral sclerosis (ALS). Here we demonstrate the generation of iPS-derived motor neurons using an optimized differentiation protocol generating a population with greater than 60% purity based on Isl1/2 and Tuj1 positive staining. Furthermore, we used this cell line to generate a TDP-43 line, equipping researchers with this valuable tool for ALS prognostics and treatment. We characterize our cells and co-cultured them with human skeletal muscle, capable of forming neuromuscular junctions in vitro. We are now exploring co-culture conditions with human iPSC-derived skeletal muscle based on our published protocol (Caron et al. 2016). Our media-based differentiation method efficiently generates contractile and fused myotubes without the need for any cell sorting or myogenic gene overexpression. Combined with our motor neurons, this co-culture platform will enable ALS drug discovery and facilitate complex disease modeling of other neuromuscular disorders.

Disclosures: B.F. Freitas: A. Employment/Salary (full or part-time):; CDI. **L.K. Fong:** A. Employment/Salary (full or part-time):; Genea Biocells US Inc. **J. Liu:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics, Inc. **B. Meline:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dyanmics Inc. **C. Chavez:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics, Inc. **T. Feaster:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics, Inc. **C. McMahon:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics, Inc. **D. Mann:** A. Employment/Salary (full or part-time):;

FUJIFILM Cellular Dynamics, Inc. **W. Wang:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics, Inc. **J. Arjomand:** A. Employment/Salary (full or part-time):; Genea Biocells US Inc. **U. Schmidt:** A. Employment/Salary (full or part-time):; Genea Biocells Us Inc. **E. Jones:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics, Inc.

Poster

675. Motor Neurons and Muscle: Motorneuron-Muscle Interface and Muscle Physiology/Biochemistry

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 675.21/QQ9

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant DA00523

Title: Plasma concentrations of alpha-pyrrolidinovalerophenone (PVP) predict the extent of motor activation after systemic administration of the drug to rats

Authors: *M. H. BAUMANN[1], H. M. WALTERS[1], J. S. ELMORE[2], D. WALTHER[1], D. M. ANDRENYAK[3], D. E. MOODY[3]
[1]Designer Drug Res. Unit, IRP, NIDA, NIH, DHHS, Baltimore, MD; [2]Johns Hopkins Med. Inst., Baltimore, MD; [3]Univ. of Utah, Salt Lake City, UT

Abstract: The synthetic cathinone alpha-pyrrolidinovalerophenone (PVP) is a widely-abused new psychoactive substance with psychomotor stimulant properties. Preclinical studies show that PVP exerts its effects by potently inhibiting high-affinity plasma membrane dopamine transporters (DAT) and norepinephrine transporters (NET), thereby elevating extracellular concentrations of dopamine and norepinephrine in the brain. No study has examined pharmacokinetics and metabolism of PVP *in vivo*. Here we examined plasma pharmacokinetics of PVP and its major metabolite 2”-oxo-PVP in male Sprague-Dawley rats fitted with surgically-implanted jugular catheters. Rats received sc injection of PVP (0.25, 0.5, 1.0 & 2.0 mg/kg) or its saline vehicle and were placed into chambers equipped with photobeams for the detection of locomotor activity. Serial blood samples were withdrawn via the catheters at 15, 30, 60, 120, 240 and 480 min post-injection and plasma was assayed for PVP and 2”-oxo-PVP using liquid chromatography coupled to mass spectrometry. We found that plasma concentrations of PVP peaked rapidly (Tmax = 15 min post-injection) and rose linearly with increasing dose (Cmax range = 13 - 149 ng/mL). The drug was quickly cleared from the circulation with a plasma half-life of about 90 min. The 2”-oxo metabolite displayed a pharmacokinetic profile similar to that of PVP, but concentrations were 30-fold lower. Motor activity induced by PVP administration was positively correlated with plasma concentrations of parent and metabolite, but *in vitro* transporter assays demonstrated that 2”-oxo-PVP does not interact with DAT or NET. Collectively, our findings demonstrate that PVP and 2”-oxo-PVP exhibit rapid pharmacokinetics in rats but the

metabolite is present at much lower concentrations and is not bioactive. Thus, behavioral activation produced by PVP is most likely due to effects of the parent compound with no involvement of its major metabolite.

Disclosures: M.H. Baumann: None. **H.M. Walters:** None. **J.S. Elmore:** None. **D. Walther:** None. **D.M. Andrenyak:** None. **D.E. Moody:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.01/QQ10

Topic: F.01. Neuroethology

Support: NSF Grant IOS 1354745
NSF Grant DOB 1359230

Title: The effect of self-generated movement on lateral line sensitivity in the toadfish, Opsanus tau

Authors: *L. S. ROGERS, JR[1,2], J. C. VAN WERT[2], A. F. MENSINGER[1,2]
[1]Univ. of Minnesota Duluth, Duluth, MN; [2]Marine Biol. Lab., Woods Hole, MA

Abstract: The mechanosensory lateral line in fishes functions to detect water displacement via the deflection of hair cells within the superficial and canal neuromasts. Previous experiments have shown that the lateral line aids in schooling behavior, rheotaxis, hearing, and predator/prey interactions. However, the effect of self-generated movement on the sensitivity of the lateral line has remained largely unknown. Prevailing hypotheses have suggested that either sensory hair cells are efferently modulated or that filtering occurs in higher order centers of the brain, thus reducing the effect of self-generated movement on the neuromasts. To test these hypotheses, microwire electrodes were inserted into the anterior lateral line nerve of Oyster toadfish (*Opsanus tau*) using an implantable micromanipulator, which allowed neural activity to be monitored for up to two weeks post-implant. Experiments measured the neural response to external stimulus, which was provided by a 50 Hz vibrating sphere or a robotic fish, during forward movement. During these experiments, the lateral line of free swimming toadfish remained sensitive to external stimuli without efferent modulation. Additionally, lateral line units did not exhibit a decrease in firing rates during movement, which indicates that the lateral line is still capable of sensing external stimuli. While efferent modulation or central filtering of self-generated movements had previously been postulated as mechanisms to allow free swimming fish to continue to detect outside stimuli, the current experiments show that at the swim speeds observed, the mechanosensory lateral line remains sensitive to external stimuli without efferent modulation or central filtering.

Disclosures: L.S. Rogers: None. **J.C. Van Wert:** None. **A.F. Mensinger:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.02/QQ11

Topic: F.01. Neuroethology

Title: Serotonergic SK channel modulation promotes adaptive optimized coding of natural stimuli

Authors: *M. G. METZEN, C. G. HUANG, M. J. CHACRON
Dept. of Physiol., McGill Univ., Montreal, QC, Canada

Abstract: Growing evidence suggests that sensory systems optimally encode natural stimuli with given statistics. As stimulus statistics vary with context, coding mechanisms must be adaptive to be efficient. Adaptation is seen ubiquitously across systems and species, and neurons can adapt their response properties to “simple”, as well as to “complex” stimulus attributes. However, the underlying mechanisms are generally poorly understood. We investigated adaptive optimized coding of electrosensory stimuli experienced by the weakly-electric fish *Apteronotus leptorynchus* in their environment. Previous results have shown that pyramidal cells optimally encode natural sensory stimuli. We thus studied whether optimized coding was adaptive to changes in stimulus statistics due to the activity of conspecific fish (Fig 1A). We presented the animal with stimuli with different statistics typically found under natural conditions and measured neuronal and behavioral performance (Fig 1B). Specifically, we varied the power law exponent describing the relationship between spectral power and temporal frequency. Neural tuning and behavioral responses were assessed using sinusoidal stimuli. We found that neurons adapted their tuning to optimally encode the new stimulus (Fig 1C, top & middle). Changes in tuning were accompanied by shifts in behavioral sensitivity to better match the new stimulus statistics (Fig 1C, bottom). Further experiments revealed that the descending signal required for adaptation reaches pyramidal neurons through serotonergic fibers emanating from the raphe nuclei (Fig 1E). This is because both neural tuning and behavioral responses did not adapt (Fig 1F) after application of the 5HT2 receptor antagonist ketanserin (Fig 1D). Our results thus reveal a novel functional role for the serotonergic system, which is very well conserved across vertebrates. Thus, the action of 5HT on tuning is likely through up- and downregulation of SK channels. Important parallels between the electrosensory and other systems imply that our results will very likely be generally applicable.

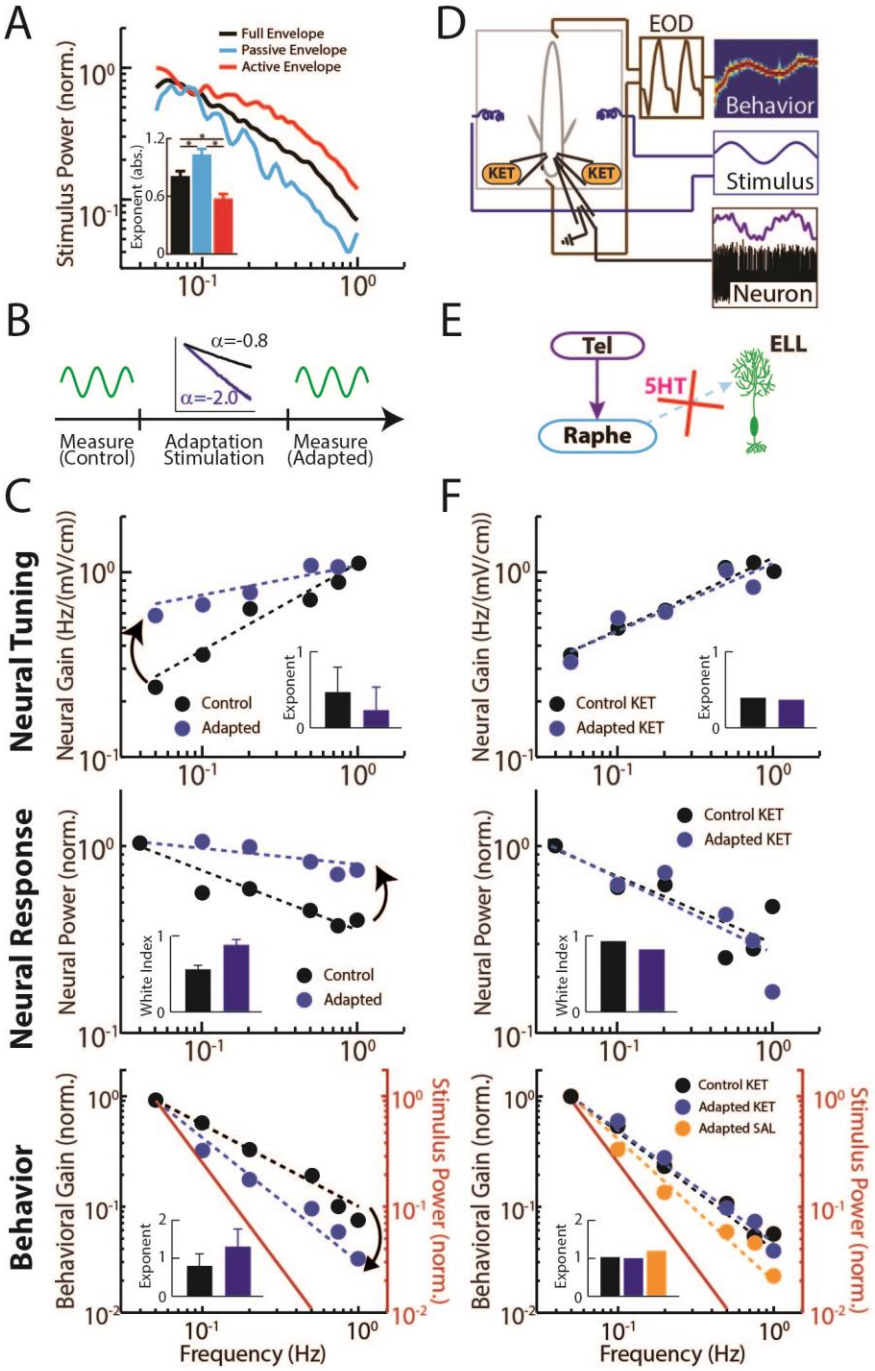


Figure 1: Optimized adaptive coding occurs in the electrosensory system. A) Power spectrum of the full movement envelope (black), during high (red) and low (cyan) activity. Inset shows the power law exponents. **B)** Stimulation paradigm showing control measurements with sinusoidal envelopes at the beginning and every 2h after stimulating with a natural movement envelope containing statistics with power-law exponent α=-2.0. **C)** Shifts in neural tuning (top), neural response via whitening (middle), and behavioral adaptation (bottom) over the course of 6h where the fish was presented with a natural stimulus with exponent α=-2.0. **D)** Schematic of experimental paradigm with ketanserin injection. **E)** Circuitry showing 5HT blockade after ketanserine application. **F)** Neural tuning (top) and response power (middle) did not shift after ketanserin (blue) injection compared to control (black) and abolishes the behavioral (bottom) adaptation (compare black and blue), while behavioral adaptation does occur for saline positive control (yellow). Insets: Power-law exponents for neural tuning and behavior and white indices for neural responses for before and after adaptation.

Disclosures: M.G. Metzen: None. **C.G. Huang:** None. **M.J. Chacron:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.03/QQ12

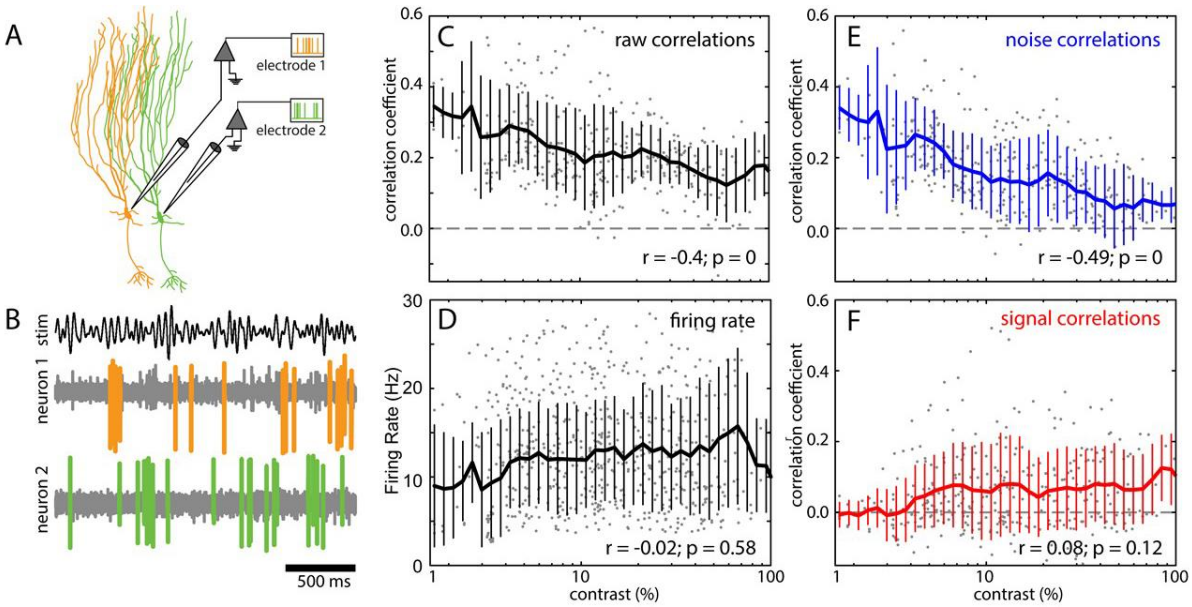
Topic: F.01. Neuroethology

Support: DFG HO 5912/1-1
Canadian Institutes of Health Research
Canada Research Chairs

Title: Correlation based stimulus encoding in electrosensory processing

Authors: *V. HOFMANN, M. J. CHACRON
Physiol., McGill Univ., Montreal, QC, Canada

Abstract: Perception and behavior are usually determined by the collective activity of large neural ensembles. Our efforts to understand population coding is however complicated by the fact that the activities of multiple neurons are not independent but correlated, a phenomenon found almost ubiquitously in the brain.
Two components contribute to correlated activity: Signal correlations quantify co-variation of the average responses of two neurons presented with different stimuli. Noise correlations quantify correlations in the response trial to trial variabilities when presented with the same stimulus repeatedly. The relation between signal and noise correlations strongly impacts information transmission. However, as noise-correlations were found to be plastic and change depending on the animal's state, attention of stimulus statistics, comprehensive knowledge of both, the functional implications on information coding and the mechanisms mediating correlation plasticity is scarce to date.
We use the weakly electric fish *A. leptorhynchus* to investigate correlation-based stimulus encoding. Our data from pairs of medullary pyramidal neurons shows that correlations (raw) decrease significantly with increasing stimulus contrast. This observation could neither be explained with changes in firing rates nor when analyzing signal correlations - both showed slight increases. Noise correlations (i.e. correlated variability) however decreased strongly thereby driving a correlation-based encoding of stimulus contrast.
Using a combination of experimental and theoretical techniques, we found that the differential activation of pyramidal neuron receptive field sub-portions can mediate changes in the balance of correlated and anti-correlated inputs thereby creating an asynchronous state. Our results are expected to have general applicability given the many parallels between the electrosensory system and mammalian visual and auditory systems.



Disclosures: V. Hofmann: None. **M.J. Chacron:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.04/QQ13

Topic: F.01. Neuroethology

Support: NSF Grant 1557895
NSF Grant 1557858

Title: Sensorimotor activity in midbrain circuits of freely swimming electric fish

Authors: *I. UYANIK[1], N. J. COWAN[2], E. S. FORTUNE[3]
[1]Johns Hopkins Univ., Baltimore, MD; [2]Dept. of Mechanical Engin., Johns Hopkins Univ. Dept. of Mechanical Engin., Baltimore, MD; [3]New Jersey Inst. of Technol., Newark, NJ

Abstract: A challenge in understanding sensorimotor systems is that they operate in a dynamic closed loop in which motor outputs stimulate sensory receptors, which, in turn, provide feedback for subsequent motor output. Our strategy to reveal mechanisms for feedback control used by animals relies on the dynamic modulation of reafferent feedback (i.e. feedback generated as a consequence of the animal's own movements). To modulate reafferent feedback, we recently built an augmented reality system for refuge tracking in weakly electric fishes. These fish swim back and forth to maintain their position within a moving refuge. The new experimental system measures the position of the fish in real time, allowing us to modulate reafferent feedback by

moving the refuge in relation to the fish's own movements.
To reveal the neurophysiological mechanisms underlying sensorimotor control in the brain, we made chronic recordings of midbrain neurons while the animal performed tracking behaviors in the augmented reality system. We implanted tetrodes into the torus semicircularis (Ts) and optic tectum (OT). Recordings in the Ts examine electrosensory activity whereas OT recordings reveal sensorimotor and multi-sensory interactions. This combination of behavioral and neurophysiological measurements allow simultaneous system identification of the sensorimotor performance of individual fish while observing the neurophysiological computations for its control.
Behavioral results show that adult *Eigenmannia* tunes its CNS controller in relation to reafferent feedback gain to maintain a constant magnitude of sensory slip between the refuge and its own sensory receptors. Our goal is to understand how this "tuning" process manifests itself through the activity of midbrain neurons.

Disclosures: I. Uyanik: None. **N.J. Cowan:** None. **E.S. Fortune:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.05/QQ14

Topic: F.01. Neuroethology

Support: NSF IOS-1456004
NSF IOS-1456558
NSF GRFP #1247192

Title: Reproductive state dependent visual sensitivity in an African cichlid fish

Authors: *J. M. BUTLER[1], S. M. WHITLOW[1], L. S. ROGERS[2], R. L. PUTLAND[2], A. F. MENSINGER[2], K. P. MARUSKA[1]
[1]Louisiana State Univ., Baton Rouge, LA; [2]Univ. of Minnesota Duluth, Duluth, MN

Abstract: Visual communication is used widely across the animal kingdom to convey crucial information about an animals' identity, motivation, reproductive status, and sex. Although it is well-demonstrated that auditory and olfactory sensitivity can change with reproductive state, fewer studies have tested for plasticity in the visual system, a surprising detail since courtship and mate choice behaviors in many species are largely dependent on visual displays. Here, we tested for reproductive state-dependent plasticity in the eye of a cichlid fish *Astatotilapia burtoni*, using behavioral, gene expression, neural activation, and electrophysiology techniques. Ovulated females had higher mRNA expression levels of reproductive neuromodulatory receptors (sex-steroids; gonadotropins) in the eye than non-ovulated females, but males had similar expression

levels independent of reproductive/social state. This increase in neuromodulatory receptors was also seen in prostaglandin F2a-induced ovulated females, but not females injected with DMSO vehicle. In addition, ovulated females were more responsive to male courtship displays, and these mate choice-like behaviors positively correlate with expression of gonadotropin system receptors in the eye. Natural and PGF2a-induced ovulated females have higher neural activation in the ganglion cell layer of the retina compared to non-ovulated females when exposed to a courting male. Using electroretinography to measure visual sensitivity in dark-adapted fish, we also found that gravid females have increased visual sensitivity at several wavelengths associated with male courtship displays compared to non-gravid females. When injected with PGF2a, gravid females ovulated and increased their spectral sensitivity compared to pre-PGF2a injection measurements. This increased sensitivity after PGF2a injections was absent in non-gravid females and males, suggesting an ovulation-triggered increase in visual sensitivity. Collectively, these data indicate that plasticity in the eye is dependent on female ovulation status, not overall female gravidity, and provides crucial evidence linking endocrine modulation of visual plasticity to mate choice behaviors in females.

Disclosures: J.M. Butler: None. **S.M. Whitlow:** None. **L.S. Rogers:** None. **R.L. Putland:** None. **A.F. Mensinger:** None. **K.P. Maruska:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.06/QQ15

Topic: F.01. Neuroethology

Support: the East Carolina University Division of Research fund and an interdisciplinary research award (IRA 591211) to F.A.I.

Title: Social regulation of dopaminergic modulation of spinal motor circuit activation in zebrafish (Danio Rerio)

Authors: *K. CLEMENTS, F. HEAGY, T. MILLER, F. ISSA
Biol., East Carolina Univ., Greenville, NC

Abstract: Adaptive motor behavior is integral for survival as animals navigate their social and physical environment. Here, we investigated how social dominance affects adaptive motor behavior while probing the neuromodulatory mechanisms that mediate activation of spinal motor circuits. Using zebrafish, we show that social status influences the activation pattern of two competing motor circuits: the Mauthner mediated escape (M-cell) and swim circuits. When paired, males form a social relationship consisting of dominants and subordinates. Using a non-invasive electrophysiological approach, we recorded field potentials generated as the escape and

swim circuits were active. Subordinates swim less and escape more than their dominant counterpart. Because of its known role in social regulation and motor control, we studied whether dopaminergic signaling underlies this behavioral shift. Using a pharmacological approach, we systemically injected L-DOPA, D1R, D2R, or D3R agonists and antagonists. Interestingly, blocking the D1R enhanced startle escape and suppressed swimming activity in dominants, mimicking subordinate behavior. Subordinates were not affected by D1R agonist or antagonist. These results correlate with brain gene expression analysis where subordinates displayed a significant decrease in D1R levels. To corroborate these findings we tested the escape and swim behaviors of homozygous D1R knockout zebrafish, which exhibited subordinate-like startle and swim activity pattern. These results suggest that dopaminergic modulation of motor activity is socially regulated and mediated via D1R. D1R is known for its excitatory signaling, yet blocking the D1R enhanced the escape response in dominants suggesting that dopaminergic modulation of the M-cell is mediated indirectly via a disinhibitory mechanism. The primary inhibitory inputs that regulate the excitability of the M-cell are GABA and Glycine. To determine which inhibitory input the D1R signaling is mediating, we administered bicuculline and strychnine. Bicuculline led subordinates to decrease their response sensitivity while dominants showed no change. If D1R was acting through GABA, it was expected that the escape sensitivity would increase in dominants, mimicking the D1R antagonist action. However, our results suggest that dopaminergic regulation of M-cell sensitivity is not mediated through GABAergic input. After strychnine administration, dominants showed an increase in escape sensitivity while subordinates showed no significant change; suggesting that D1R influences the M-cell through Glycine. Our results highlight the impact of social interactions on CNS function.

Disclosures: K. Clements: None. **F. Heagy:** None. **T. Miller:** None. **F. Issa:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); the East Carolina University Division of Research fund and an interdisciplinary research award (IRA 591211).

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.07/QQ16

Topic: F.01. Neuroethology

Title: Neuronal representation and sensorimotor integration of auditory cues in zebrafish larva

Authors: *M. PRIVAT[1], S. ROMANO[2], A. JOUARY[3], T. PIETRI[4], J. BOULANGER-WEILL[5], N. ELBAZ[6], D. SOARES[7], G. SUMBRE[4]
[1]Inst. De Biologie De L'Ens, Paris, France; [2]IBIOBA-Max Planck Partner Inst., Buenos Aires, Argentina; [3]Champalimaud, Lisbon, Portugal; [4]Ecole Normale Superieure, Paris, France;

[5]IBENS INSERM U1024, Paris, France; [6]Inst. de Biologie de l'ENS, Paris, France; [7]Biol. Sci., NJIT, Newark, NJ

Abstract: Vertebrates can pick up cues from their environment through their sensory systems and integrate this information to produce relevant, context-dependent behavior.
While we are able to map the representation of sensory inputs and motor commands in the brain by looking at the correlation between the occurrence of stimuli or behavior and neural activity, the way sensorimotor integration is performed still remains an open question.
To address this question, we used two-photon calcium imaging in intact, behaving zebrafish larvae expressing the genetically encoded calcium indicator GCaMP5. We monitored neural activity elicited by pure tones (150 to 1000 Hz) across large portions of the brain with near single-cell resolution, while simultaneously recording motor activity with a high-speed camera.
We observed stimulus-related neural responses in the octaval nuclei and torus semicircularis, in agreement with previous studies. We found 4 classes of neurons with different tuning properties. Stimuli with frequency between 150 and 450Hz were able to elicit motor activity, which was not restricted to the mauthner-mediated escape response.
We classified the neurons according to their correlation with stimulus presentation and behavioral output and identified regions which could mediate the sensorimotor transformation via a gating mechanism.

Disclosures: M. Privat: A. Employment/Salary (full or part-time):; Université Pierre et Marie Curie. **S. Romano:** None. **A. Jouary:** None. **T. Pietri:** None. **J. Boulanger-Weill:** None. **N. Elbaz:** None. **D. Soares:** None. **G. Sumbre:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.08/QQ17

Topic: F.01. Neuroethology

Support: MOST 105-2311-B-007 -013 -MY2

Title: Altruistic allogrooming in subordinate male mice

Authors: *T.-H. KUO, Y.-S. SU
Inst. of Systems Neuroscience, Natl. Tsing, Hsinchu, Taiwan

Abstract: Animals perform a wide range of social behaviors for survival and reproduction. Understanding these behavior may provide a framework of social interactions in human and eventually help us to elucidate abnormalities in social behaviors under various psychiatric disorders. Allogrooming, or social grooming, is defined as grooming behavior between members

of the same species and can be widely observed throughout animal kingdoms. This behavior plays an important role in social bonding and is generally believed to be an altruistic behavior because groomers face several immediate costs to benefit recipients. Although allogrooming has been documented in mice, the functions and mechanisms have never been well characterized due to intensive male-male aggression, which limits the observations of other social behaviors during resident-intruder assay. By comparing dominant and subordinate males under resident-intruder assay, we found that subordinate males lose their aggression but mainly perform allogrooming during interaction with intruders while there is no change in other social behaviors. Covering exotic materials, like mineral oil, on an intruder significantly enhanced the allogrooming behavior from a groomer (resident), supporting the function of allogrooming for hygienic purpose. We also observed increase of immobile time of intruder during allogrooming interaction, suggesting that grooming recipients are directly benefited from this social interaction. Our study showed that allogrooming in mice is altruistic and can be easily observed in subordinate animals. This study established a new platform to investigate the biological mechanisms of altruistic behaviors for future study.

Disclosures: T. Kuo: None. **Y. Su:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.09/QQ18

Topic: F.01. Neuroethology

Support: ZIM KF3449301TS4
ZIM KF2158702TS4

Title: Multiple running wheels with ID sensors for group-housed mice

Authors: *C. K. JUNG[1], O. JANKE[2], J. FÜNER[2], Y. WINTER[3]
[1]Phenosys Gmbh, Berlin, Germany; [2]Preclinics GmbH, Potsdam, Germany; [3]Humboldt Univ. - Inst. Biologie, Berlin, Germany

Abstract: Mouse models of neurological disorders, such as multiple sclerosis and Parkinsons disease, and models of pain exhibit marked deviations in several parameters of voluntary wheel running activity. Thus, wheel running assays serve to diagnose disease progression and treatment outcome. Typically, mice are kept singly in their wheel cages even for extended periods of time. For ethical reasons group housing of mice would be highly preferable. We present a novel system where wheel running cages are mounted in a regular cage rack. The cages are interconnected so that mice can move between them. Mice carry subcutaneous RFID chips for individual identification. ID sensors placed outside the cages but next to a cage‘s wheel detect

the identity of the mouse that uses the wheel. Thus, any wheel running can be assigned to an individual mouse. Wheel running of individual mice can be scored irrespective of the specific wheels used by a mouse. This novel system allows keeping mice in groups but still obtain individual records of running activity. We demonstrate the great potential of this novel method with data from a mouse model of muscle paralysis.

Disclosures: C.K. Jung: A. Employment/Salary (full or part-time):; C Jung is employed at PhenoSys. **O. Janke:** A. Employment/Salary (full or part-time):; O Janke is employed at Preclinics. **J. Füner:** A. Employment/Salary (full or part-time):; J Füner is CEO of Preclinics. **Y. Winter:** A. Employment/Salary (full or part-time):; Y Winter is CEO of PhenoSys..

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.10/QQ19

Topic: F.01. Neuroethology

Support: R01NS097762
R01AA020073
T32NS041231
T32NS041218
R01NS097762-S1
KL2TR001432

Title: Looming threat as an ethological stimulus for use in anxiety studies

Authors: *B. L. AGUILAR[1,2,3], J. TOIB[1,4], L. MALKOVA[2,3], P. A. FORCELLI[2,3]
[2]Dept of Pharmacol., [3]Interdisciplinary Program in Neurosci., [4]Dept of Biol., [1]Georgetown Univ., Washington, DC

Abstract: Rapidly approaching visual stimuli (looming objects) are known to evoke unconditioned defense responses across species. From lampreys to monkeys, such responses to predator approach are important for species survival and appear to be highly evolutionarily conserved. A subcortical visual threat processing pathway containing the superior colliculus (SC) has been described in rodents as a structure important for visual loom response. The SC receives multimodal sensory information, including visual information via retinal relay, and mediates reflex-like behaviors, orienting, avoidance, cowering, escape, and defensive vocalizations. Response to visual loom falls under the umbrella of threat reactivity in which the SC appears to play a critical role. Although components of the circuitry underlying unconditioned response to a looming stimulus have been elucidated, pharmacological studies showing modification of the behavior itself have yet to be completed. Similarly, aside from a single study investigating an

autism-like mouse mode, no behavioral outcomes from disease or disorder models have been described. Here we describe a modified version of the looming threat task, Forced Loom, where no escape route is available using Sprague-Dawley (SD) rats. We characterized several variables of interest: stimulus specificity (loom vs. reverse loom), habituation (repeat loom exposure), context-dependence (reinstatement of freezing), pharmacological sensitivity (anxiogenic/ anxiolytic drug effects in naïve and habituated rats), and ethological priming effects (cat odor, female rat odor). We observed strong freezing in response to an expanding disk, but not to control stimuli [I.e., a grey screen, a contracting disk] during the loom period ($P<0.01$, 2-way ANOVA, pairwise comparisons) and during the post-loom period ($P<0.01$), fast habituation to the stimulus (by 2nd loom, $P<0.01$), and a lack of context-dependent reinstatement (1st v. 4th loom, $P=0.68$). Interestingly, we found that while administration of diazepam to naïve SD rats significantly reduced freezing ($P<0.01$), administration of GABA inverse agonist FG-7142 displayed not change to behavior ($P=0.08$). We report sex differences in their responses in this task. Studies are currently underway to examine both the plasticity of this behavior using ethological priming stimuli and any strain-specific differences between SD and Long Evans rats.

Disclosures: B.L. Aguilar: None. **J. Toib:** None. **L. Malkova:** None. **P.A. Forcelli:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.11/QQ20

Topic: F.01. Neuroethology

Support: NSF IIS-1427419

Title: Why animal wiggle their sensors when following signals

Authors: *C. CHEN[1], M. A. MACIVER[2]
[1]Biomed. Engin., [2]Biomed. and Mechanical Engin., Northwestern Univ., Evanston, IL

Abstract: Movement and sensing work fundamentally in synergy. Animals move around to gather information and the new information guides the animal to initiate new movements. Sensory organs such as eyes, ears, and noses -- and the bodies they are attached to -- are constantly on the move as animals progress from exploring, searching, tracking, and finally, physical engaging with targets of interest. Surprisingly, an animal searching for either a stationary or a moving target not only orients its sensory organs to the target, but also wiggles them around the axis to the target. These controlled movements have been observed across a diverse range of animal lineages, from marine snails to humans. What is the underlying objective of these movements? We re-analyzed past movement data from mammalian olfactory tracking, along with new data on electrosensory tracking, to quantify key features of sensor wiggle. With

our analysis, we demonstrate a new finding that sensory wiggle amplitude decreases as sensory signals transition from weak to strong while animals close in on their target. Here we propose an ergodic information harvesting strategy, a novel theoretical framework that naturally reproduces these wiggle motions as well as their variation with changes in signal strength. The proposed model uses an information-theoretic approach to close the movement and sensing loop by planning trajectories for the information gathering organs to sample space proportionate to the expected information gain. The behavioral signatures of ergodic information harvesting -- including small oscillatory movements of sense organs sometimes interpreted as contributing error to subsequent neural processing -- are markedly different from alternative models proposed for active sensory movements such as infotaxis. In addition, by examining the effect of attenuating the wiggles generated by the algorithm on simulated tracking, we provide quantitative evidence that sensor wiggle enhances tracking performance. These results demonstrate that exploratory motions prior to signal detection and exploitative motions following detection do not require different mechanisms, but rather can be explained by the emergent features of ergodic information harvesting. Our normative framework provides a new perspective in the effort to understand sensorimotor integration in animals behaving in complex environments with uncertainty.

Disclosures: C. Chen: None. **M.A. MacIver:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.12/QQ21

Topic: F.01. Neuroethology

Support: Biotechnology and Biological Sciences Research Council (BB/P007201; JFL)
Action on Hearing Loss (G77; JFL)
Gatsby Charitable Foundation (GAT3528; MS) (GAT3212; JOK)
Simons Foundation (SCGB323228; MS)
UCL Excellence Fellowship (JP)
Wellcome Trust (090843/C/09/Z, 090843/D/09/Z, 203020/Z/16/Z; JOK)

Title: The mousecam: A miniature head-mounted camera system for freely moving mice integrates detailed behavioural monitoring with multichannel electrophysiology

Authors: *M. SAHANI[1], J. POORT[2], A. F. MEYER[1], J. O'KEEFE[3], J. F. LINDEN[4]
[1]Gatsby Computat. Neurosci. Unit, [2]Sainsbury Wellcome Ctr., [3]Sainsbury Wellcome Ctr. and Dept. Cell & Devel. Biol., [4]Ear Inst. and Dept. Neurosci. Physiol. & Pharmacol., Univ. Col. London, London, United Kingdom

Abstract: A major goal in neuroscience is to understand how neural circuits integrate a wide range of inputs to produce flexible and adaptive behaviours in natural settings. This requires detailed monitoring of both neural activity and behavioural variables while animals interact with their environment. An extensive toolkit for neural circuit recordings and manipulations makes the mouse a powerful model organism for systems neuroscience. However, detailed monitoring of behaviour in freely moving mice remains a major challenge.
Here, we report the development of a lightweight head-mounted camera system that we combine with motion sensors and multichannel neural recording devices to simultaneously monitor eye position, pupil dilation, and whisking along with head motion and neural activity in unrestrained, freely behaving mice. The system generates stable video output with image movements of less than 1 pixel (40 microns) in ~99% of the frames, even during active behaviours such as running and grooming. Moreover, the system has minimal effect on mouse behaviour, thereby enabling studies of natural ethology.
We demonstrate the potential of the system in a series of experiments in freely moving mice. First, we show that whisking frequency and pupil size vary systematically with behavioural state and that these changes are correlated with neural activity, thereby generalizing to freely moving mice and natural behaviours results previously obtained in head-restrained animals (e.g., McGinley et al. *Neuron* 2015). Second, we demonstrate that a large fraction of variability in eye position in freely moving mice is explained by head movements, as has also been observed in rats (Wallace et al. *Nature* 2013). Our data further indicate that mice stabilize their gaze with respect to the horizontal plane, and that this stabilization does not depend on visual input. Third, we demonstrate that neural activity in primary visual cortex is strongly modulated by self-generated head movements, even in the absence of visual input. This effect was not explained by whisking or variability in eye movements. These results illustrate how the new system can give novel insights into the interactions between different behaviours and their relation with neural activity.
The head-mounted camera system is open-source and we provide all required software and design files. Furthermore, the system is modular and therefore could be integrated with alternative methods for recording neural activity and/or combined with technologies for optogenetic manipulation of neural circuits during behavioural monitoring.

Disclosures: M. Sahani: None. **J. Poort:** None. **A.F. Meyer:** None. **J. O'Keefe:** None. **J.F. Linden:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.13/QQ22

Topic: F.01. Neuroethology

Support: NSF #1743475

Title: Understanding the role of sensory feedback on a robotic platform during peristaltic locomotion

Authors: *A. KANDHARI[1], H. J. CHIEL[3], R. D. QUINN[1], K. A. DALTORIO[2]
[1]Mechanical and Aerospace Engin., [2]Mechanical Engin., Case Western Reserve Univ., Cleveland, OH; [3]Case Western Res. Univ., Cleveland, OH

Abstract: Earthworms locomote using traveling waves of segment contraction and expansion. Because of the hydrostatic coupling, as the diameter of a segment increases, its length decreases. Segments can also bend. The mechanics of the body result in a large range of body shapes that both comply with the environment and contribute to directed locomotion. During the crawling movements of earthworms, sensory feedback provides the animal with an ability to adapt to different types of environmental perturbations. Mechanosensory organs and stretch, touch, and pressure receptors are the feedback sources in earthworms that allow the body to contort and adapt to its surrounding environment. Here, we present a robotic platform for exploring the role of sensory feedback to control peristaltic locomotion in constrained environments. Inspired by earthworms, we designed and constructed a new robot: Distributed-Sensing Compliant Worm (DiSCo-Worm) Robot. DiSCo-Worm is equipped with 36 Force Sensing Resistors (6 per segment) that allow the robot to detect external constraints and 12 flexible stretch sensors (2 per segment) that allow for tracking the shape of the robot. We contrast the ability of the robot to navigate in constrained spaces using an open-loop, time-based controller and a closed-loop sensory feedback controller. The results indicate that when the robot can sense its environment and its internal state (longitudinal extension of each segment), it uses this information to determine whether to expand, contract or anchor each segment. Using the closed-loop controller, the robot is able to adapt to its environment and reduce forward slip, which accounts for 58% of the total motion in open-loop control.

Disclosures: A. Kandhari: None. **H.J. Chiel:** None. **R.D. Quinn:** None. **K.A. Daltorio:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.14/QQ23

Topic: F.01. Neuroethology

Support: NSF GRFP
HHMI

Title: Preserved gene coexpression networks between human cortex and songbird pallium

Authors: *G. GEDMAN[1], B. HAASE[2], O. FEDRIGO[2], E. D. JARVIS[3]
[1]The Lab. of Neurogenetics and Language, The Rockefeller Univ., New York, NY; [2]Vertebrate Genome Lab., [3]The Lab. of Neurogenetics of Language, Rockefeller Univ., New York, NY

Abstract: The six-layered mammalian neocortex and the nuclear avian pallium bear little structural resemblance, presenting a challenge for comparing the neuroanatomical substrates of complex behavioral traits across species. A major step towards understanding the avian-mammalian neuroanatomical relationship has been resolving the cell-type homologies between these lineages. Using shared neural connectivity, gene expression, and physiology, some studies suggest a one-to-one homology between the different mammalian cortical layers and different avian pallial subdivisions (nuclear-to-layer hypothesis), while others argue that the mammalian neocortex is wholly different from the avian pallium (independent evolution hypothesis)[1]. A limitation of these studies is that a small number of genes have been analyzed leading to underpowered interspecies comparisons. Here we used next-generation RNA sequencing (RNASeq) to assess the entire transcriptome within and between songbird pallial regions (zebra finch) laser captured in our lab and human cortical layers isolated by the Allen Institute for Brain Science. Using clustering analyses of significantly differentially regulated genes, we showed that the avian ventral mesopallium is nearly identical in its transcriptome profile to what is known as the dorsal mesopallium. Further, we found that the hyperpallium and nidopallium are nearly identical, suggesting shared developmental origins of these subdivisions. In the human brain, layer 4 transcriptome data were not easily distinguished from the other cortical layers, presumably due to inaccurate dissections, but we did find distinct profiles for the upper and lower layers. For comparisons between species, we used weighted gene coexpression network analysis (WGCNA)[3] and identified ~10-20 coexpression modules per species, each containing ~100 genes, with evidence of module preservation across species. The module with the highest significantly preserved expression ($Z_{summary}$ = 26.11) was composed of ~2500 genes that associated the avian arcopallium and deep cortical layers 5 and 6 in humans. Gene ontology analysis found this module is enriched for genes involved in anatomical organ development and cell-fate determination. The next highest module, with fewer genes, associated the avian mesopallium regions with upper cortical layers 2/3 of humans. Together, these results support the nuclear-to-layer hypothesis of vertebrate brain evolution. This work highlights the presence of shared gene networks across songbird and human, species separated by more than 300 million years, and provides hundreds of candidate genes for testing conserved functionality.

Disclosures: G. Gedman: None. **B. Haase:** None. **O. Fedrigo:** None. **E.D. Jarvis:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.15/QQ24

Topic: F.01. Neuroethology

Support: NSF Career 1551526

Title: Modeling visual perception, learning, and memory of wood ant navigation in naturalistic environments

Authors: *A. J. MENDOZA, D. D. LENT
Biol., California State Univ. Fresno, Fresno, CA

Abstract: A number of experiments have revealed how different visual features are used to guide familiar foraging routes in wood ants. Using these data, we have developed algorithms to extract visual features that ants use for guidance from panoramic scenes. We created a computational foraging model in the MATLAB computer program to simulate navigation in procedurally generated environments where the visual cues could be precisely characterized. In these environments, our algorithms extracted and stored the visual cues that were available during a single Levy-walk foraging event. Following a random foraging event, the success on subsequent return bouts using the stored information was examined. To explore how to best store information we simulated the Levy-walk foraging events over various sampling points (1000-10000) and implemented linear or exponential decay in the networks storing the information. Our data suggests that the optimal strategy is to sample and store between 1000 and 2000 points along the walk, with a network subjected to exponential decay. These parameters resulted in a stored representation that allowed the simulated ant to best find the goal on subsequent foraging bouts. We then produced several novel random foraging walks to the same goal location. The subsequent walks for these foraging events had similar success while taking different paths back to the goal, demonstrating idiosyncratic routes were formed and that sufficient information was stored regardless of where in the environment the random path searched before reaching the goal location. Additionally, we explored how repeated subsequent walks updated and modified memory to produce more robust walks over time. Our model has also been used to predict how changes in the environment would disrupt navigational success by producing subsequent walks after a portion of the objects in the virtual world are removed. The results of these simulations have provided insight into the mechanisms involved in prioritization and perception of visual information, it supports that ants need only processes relevant cues intermittently and they do not continually process visual information. Additionally, it has let us investigate how learning and storage of spatial information can be optimized in simple networks and nervous systems.

Disclosures: A.J. Mendoza: None. **D.D. Lent:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.16/QQ25

Topic: F.01. Neuroethology

Support: NSF Career award 1453167
Arnold & Mabel Beckman Foundation
NIH Grant 1R01NS097547-01A1

Title: What does it mean to be a tactile specialist? Lessons from peripheral anatomy and central processing in 7 species of waterfowl

Authors: *E. R. SCHNEIDER[1], C. R. LATTIN[2], E. O. ANDERSON[1], M. MASTROTTO[1,3], J. E. BROWN[2], E. O. GRACHEVA[1,3], S. N. BAGRIANTSEV[1]
[1]Cell. and Mol. Physiol., [2]Dept. of Radiology and Biomed. Imaging, [3]Neurosci., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Waterfowl of the Anatidae family exist in a variety of habitats, changing their diet during development, migration, and breeding. Depending on time and location diving ducks prefer different foods from dabbling ducks, and rely to differing extents on tactile or visual foraging strategies. It has been shown that across orders of birds the size of brain regions that process tactile or visual information correlates well with reliance on touch or vision for foraging (Gutiérrez-Ibáñez et al., 2009; Dubbeldam, 1990). Likewise, bony "pits" in the bill are also present in bills of many tactile specialist birds. This led us to ask whether anatomical and functional differences in the trigeminal system innervating the bill can be detected in closely related species of Anatidae with different foraging strategies. Since ducks are precocial we performed these tests shortly before hatching. Our sample consisted of embryos at the "exterior pip" stage from seven species including dabbling ducks from genera Aix and Anas, and diving ducks from genera Aythya, Mergini, and Oxyurini. We measured the number of bony pits in the bill using microCT, the percentage of trigeminal ganglia (TG) neurons expressing the mechanosensitive ion channel Piezo2 using *in situ* hybridization, and the number and sensitivity of acutely-dissociated TG neurons responding directly to mechanical stimulation by patch-clamp electrophysiology (n=2-3 embryos, 40-178 cells per species). We compared these parameters with the relative size of brain regions receiving tactile input from TG from the literature. The number of bony pits was not significantly correlated with the number of mechanosensitive neurons, neuronal sensitivity, or Piezo2 expression, suggesting that in these species bony pits are not a good predictor of tactile acuity. We hypothesized that neurons obtained from dabbling ducks from the genus Anas would be more numerous and sensitive than those of diving ducks from genus Mergini. However, the number and sensitivity of mechanosensitive TG neurons varied widely within species obtained from both genera. For instance, *A. pekin* was more sensitive than *A. rubripes* on both measures, confirming our prior reports (Schneider et al., 2017, Schneider et al., 2014). Surprisingly, TG neurons from Ruddy ducks (*O. jamacensis*) were most sensitive to touch but had the smallest number of neurons expressing Piezo2, suggesting the presence of an alternative mechanotransducer. Overall our findings reveal that across these species anatomical organization is not highly predictive of functional sensitivity, suggesting adaptation to tactile foraging in Anatidae can occur by a variety of strategies.

Disclosures: E.R. Schneider: None. **C.R. Lattin:** None. **E.O. Anderson:** None. **M. Mastrotto:** None. **J.E. Brown:** None. **E.O. Gracheva:** None. **S.N. Bagriantsev:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.17/QQ26

Topic: F.01. Neuroethology

Title: Bite force in the naked mole-rat (Heterocephalus glaber)

Authors: B. W. CAIN[1], D. KUKLA[2], J. KODURI[3], *D. K. SARKO[4]
[1]Anat., Southern Illinois Univ. Sch. of Med., Carbondale, IL; [3]Computer Engin., [2]Southern Illinois Univ., Carbondale, IL; [4]Dept. of Anat., Southern Illinois University, Sch. of Med., Carbondale, IL

Abstract: Naked mole-rats (*Heterocephalus glaber*) are subterranean rodents from the family Bathyergidae. The naked mole-rat has emerged as a leading model for studies of dentition due to behavioral reliance on the incisors for object manipulation, grasping, exploration, and navigation of the environment. Naked mole-rats utilize their incisors for feeding, for chisel-tooth digging of complex tunnel systems, and for social interactions (or defense) in their eusocial colony structure. In addition, the naked mole-rat exhibits remarkably expanded central nervous system representations with modular organization devoted to tactile inputs from the dentition. Although previous studies have shown that naked mole-rats have relatively wider and taller skulls (attributes associated with greater bite force; McIntosh and Cox, 2016), in addition to impressive masticatory musculature (Cox and Jeffery, 2011; Cox and Faulkes, 2014), no studies to date have directly measured bite force in this species. In the current study, we assessed naked mole-rat bite force in relation to skull and body measures as well as each animal's position within the social hierarchy (i.e., the dominant queen and subordinate males and females). Individual animals were placed in an enclosure similar to their home cages and connected to a tunnel-like tube that provided access to the bite force sensor. Animals were permitted to freely interact with the sensor, which they were more motivated to bite when it was blocking a potential exit route. Bites were recorded using a piezo-resistive force sensor (Tekscan Flexiforce sensor coated in Plasti Dip) connected to a Raspberry Pi (Model B) for data recording of each behavioral session and subsequent analyses. We hypothesized that the naked mole-rat's bite force would exceed that predicted by its body size due to the behavioral importance and specialization of the naked mole-rat incisors. Altogether, these studies provide insight into the differences in bite force across species, and the role that social and ecological factors might play in the evolutionary relationship between bite force performance and underlying anatomical structures.

Disclosures: B.W. Cain: None. **D. Kukla:** None. **J. Koduri:** None. **D.K. Sarko:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.18/RR1

Topic: F.01. Neuroethology

Support: UIC Faculty of Science Award

Title: Short-term inflammatory pain in the African naked mole-rat is driven by P2Xr and can be attenuated by the endocannabinoid system

Authors: *B. M. BROWE, C. RAMIREZ, T. J. PARK
Biol. Sciences- Neurobio., Univ. of Illinois At Chicago, Chicago, IL

Abstract: African Naked Mole-Rats (NMR) are highly social long-living mammals (lifespans reaching >30 years) whose fossorial lifestyle comes with a multitude of challenges. One predominant hurdle to adapting to life underground in large colonies (as many as 200 animals) is that the habitat becomes hypoxic and CO2 levels increase. Previously, our lab has shown that NMR have developed mutations in their Nav1.7 voltage gated Na+ channel, to become impervious to the painful acidosis caused by increased CO2. In addition, NMR have a mutated peripheral substance P promoter region, eliminating the chemical messanger from the presynapse of sensory nerve C-fibers making them impervious to capsaicin. These mutations completely eliminate pain response from capsaicin and CO2; however, they do not affect mechanical pain such as the tail pinch and, most interestingly, only partially reduce short-term inflammation from assays including the formalin test. This study aimed to characterize the remaining functionality of the peripheral pain pathway for short-term inflammation in the NMR. Here, we show that the NMR's attenuated pain response to formalin can be rescued with Substance P replacement to the spinal cord triggering activation of TRPV1 receptors. Additionally, the inflammatory response to formalin is significantly reduced after P2X3r antagonism. P2X3r has been implicated as a target for cannabinoids in pain attenuation. The endocannabinoid system is a major regulator of synaptic signals through retrograde
inhibition and manipulation of the cannabinoid system has shown promise in medical treatments of pain. However, cannabinoids have also been shown to have a high affinity to TRPV1. The NMR offers a unique ability to test the effect of Cannabinoid Receptor 1 (CB1r) activation in pain attenuation for the P2X3r pathway in a wild type animal without interference from the peripheral TRPV1 pathway. We found that there is a significant attenuation to formalin pain when given WIN55, an agonist to CB1r. Moreover, this pain attenuation is to a greater degree than that of WT mice indicating that this pathway is an important component of NMR pain reduction. Our results indicate that, while NMR are completely unaffected by capsaicin they retain a functioning P2X3r pathway that can be modified by cannabinoids.

Disclosures: B.M. Browe: None. **C. Ramirez:** None. **T.J. Park:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.19/RR2

Topic: F.01. Neuroethology

Support: Human Frontier Science Program (LT000220/2018-L)
National Science Foundation IOS-1010193 and IOS-1460149
Office of Naval Research N00014-12-1-0339
Air Force Office of Scientific Research FA9550-14-1-0398

Title: Neural mechanisms for discrimination of communication and echolocation calls in the big brown bat (Eptesicus fuscus)

Authors: *A. SALLES[1], S. MACIAS[2], H. SUNDAR[3], M. ELHILALI[3], C. F. MOSS[3]
[1]Psychology and Brain Sci., [2]Dept. of Psychological and Brain Sci., [3]Johns Hopkins Univ., Baltimore, MD

Abstract: Auditory scene analysis is crucial for species that rely on sound to navigate their environment. Bats are auditory specialists that use echoes from their own vocalizations to build a scene of their surroundings. At the same time, these social animals live in roosts and use their vocalizations to communicate with conspecifics. Important advances have been made in understanding the neural underpinnings of echolocation, but far less is known about the mechanisms supporting acoustic communication. In big brown bats (*Eptesicus fuscus*) call structure, along with behavioral context, appears to determine the function of acoustic signals. Specifically, FM bouts are emitted by males in a competitive foraging environment and are hypothesized to have a food claiming function. Though these calls differ in behavioral relevance with conspecific echolocation calls, they overlap in spectro-temporal features. This raises the question of how stimulus content is processed to support discrimination of communication calls and echolocation calls. We are investigating the neural mechanisms that enable the discrimination of natural stimuli that overlap in spectro-temporal features. Using 16-channel silicon probes in awake restrained animals, we compare responses of single neurons in the Inferior colliculus (IC) to playbacks of acoustic signals used by bats for spatial orientation and social communication. FM Bouts elicited strong responses in a subpopulation of neurons, while the same neurons showed weak or no responses to sequences of echolocation calls that matched the timing of the communication calls. This result was consistent in both female and male bats, supporting previous data that showed no sex difference in behavioral responses to these social calls. STRF analysis was performed to further understand the stimulus features that contribute to the selectivity of these midbrain neural responses.

Disclosures: A. Salles: None. **S. Macias:** None. **H. Sundar:** None. **M. Elhilali:** None. **C.F. Moss:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.20/RR3

Topic: F.01. Neuroethology

Support: NSF IOS-1010193
NSF IOS-1460149
ONR N00014-12-1-0339
AFOSR FA9550-14-1-0398

Title: Inactivation of the superior colliculus alters orienting behavior in the echolocating bat

Authors: *B. L. BOUBLIL[1], M. J. WOHLGEMUTH, III[2], C. F. MOSS[2]
[1]Psychological and Brain Sci., [2]Johns Hopkins Univ., Baltimore, MD

Abstract: The midbrain superior colliculus (SC) is a multimodal, laminated structure implicated in sensorimotor integration and goal-directed orienting movements of the eyes, head and ears. Past work has identified specializations in the SC of the echolocating bat for audiomotor integration, namely 3D tuning of auditory neurons and vocal-motor activity preceding each sonar call. The success of bat echolocation depends on adaptive orienting behaviors in response to information carried by echo returns. For example, a bat adjusts sonar call duration and interval as it tracks, approaches, and prepares to capture prey. The capture phase, characterized by a call rate of ~150 Hz, is commonly referred to as the terminal buzz. Here, we investigated the role of the SC in the echolocating bat's temporal coordination of adaptive vocal behaviors for precise sonar target tracking. In this experiment, big brown bats (*Eptesicus fuscus*) were trained to track a moving tethered insect from a platform. The target approached the bat with one of two different trajectories, simple linear motion directly towards the bat or complex back and forth motion, before arriving at the bat's position. Additionally, two stationary clutter objects were positioned symmetrically on either side of the moving target at a distance of 70 cm and an angular offset of 10º from the target's path. The bat's echolocation behaviors were studied under simple or complex target motion trajectories, and in the presence or absence of clutter objects. Muscimol, a GABA agonist, or saline was infused bilaterally into the SC. We found a significant increase in the rate of vocal production following SC inactivation with muscimol. We also found that the terminal buzz onset occurred earlier (i.e. when the target was further from the bat) in muscimol treatment trials, suggesting a disruption in the bat's coordination of sonar call parameters with target distance. And lastly, we found an increase in the duration of the terminal buzz, preceding target capture. Taken together, these data suggest that the SC plays a role in

temporal coordination of sonar orienting behaviors.
Supported by NSF IOS-1010193 and IOS-1460149; ONR N00014-12-1-0339; and AFOSR FA9550-14-1-0398.

Disclosures: B.L. Boublil: None. **M.J. Wohlgemuth:** None. **C.F. Moss:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.21/RR4

Topic: F.01. Neuroethology

Title: Claustrum and endopiriform nucleus in the fruit bat

Authors: *R. ORMAN[1], R. KOLLMAR[2], M. STEWART[1]
[1]Physiology&Pharmacology, [2]Cell Biol., SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: The Seba's short-tailed bat, Carollia perspicillata, a fruit bat, is an interesting animal to offer insights into the question of whether claustrum and endopiriform nucleus are anatomically and functionally close enough to each other to warrant sub-naming of a single structure or if they show enough structural or functional independence to preserve their separate naming. A strong argument that claustrum and endopiriform nucleus are closely related enough to be considered as subregions themselves of a parent structure comes from immunohistochemistry with relatively claustrum-specific markers, such as latexin. However, in anatomical studies with non-specific neuronal markers such as NeuN, the sizes, shapes, density, and orientation of cells differentiate the claustrum from the endopiriform nucleus. In NeuN-stained material, the natural boundary between the claustrum and endopiriform nucleus is evident as an abrupt shift from densely packed claustral cells located dorsally to the distinctly lower density packing of endopiriform neurons located ventrally. Dorsomedial and ventrolateral subregions based on size, shape, and cell density can be visualized in endopiriform nucleus. The most impressive definition of claustrum as separate from the endopiriform nucleus in Carollia brain comes from labeling cells of both regions for calcium binding proteins such as parvalbumin, calretinin, and calbindin. In adult Carollia, parvalbumin-expressing neurons are found in the claustrum, but not in the endopiriform nucleus. In claustrum, parvalbumin-immunoreactive (ir) and calbindin-ir neurons are the most common for calcium binding proteins (among parvalbumin, calretinin, calbindin), and account for close to 10% of all cells based on DAPI labeling of cell nuclei. By contrast, calretinin-ir neurons are absent from claustrum. Calretinin-ir neurons are located in significant numbers along the ventral edge of the endopiriform nucleus, forming a partial ring around the ventrolateral portion of the endopiriform nucleus. Much of the connectivity data available from other species is not yet available for the

bat, but based on the histological and physiological data that are available, we believe the bat brain offers a strong case for separate identities of claustrum and endopiriform nucleus.

Disclosures: R. Orman: None. **R. Kollmar:** None. **M. Stewart:** None.

Poster

676. Neuroethology: New Insights in Sensory and Motor Systems

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 676.22/RR5

Topic: F.01. Neuroethology

Support: NSF CRCNS IOS1460149
AFOSR FA9550-14-1-039
ONR N00014-12-1-0339
ONR N00014-17-1-2736

Title: Sensorimotor activity in the superior colliculus of the echolocating bat as it moves freely in 3D space

Authors: *M. J. WOHLGEMUTH, III[1], N. B. KOTHARI[2], C. F. MOSS[2]
[2]Psychological and Brain Sci., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: As animals move about the world, they navigate through 3D space, localizing objects, and steering around obstacles. Visual and auditory localization of objects, and attention to their features, has been studied primarily in restrained subjects performing simplified tasks. If we are to gain an understanding of brain function in more real-world settings, we must study animals moving through space, sensing objects in their environment, and reacting to dynamic stimuli. Our research investigates sensorimotor events in the central nervous system of animals engaged in natural and adaptive behaviors. Specifically, we have recorded from the midbrain of flying, echolocating bats as they navigated through a 3D environment, sensing and reacting to physical obstacles along their flight path. We performed wireless neural recordings in the superior colliculus, a midbrain structure conserved across vertebrates (optic tectum in non-mammals), which is integral to the representation and use of egocentric sensory cues to drive orienting behaviors. In animals that use vision, such as primates, the SC guides eye movements to visual targets. The SC is also involved in auditory orientation and shows activity in the echolocating bat related to its sonar orienting behaviors. In our experiment, bats flew freely in a multimedia test room, and we recorded from three different functional classes of neurons in the SC: sensory neurons that showed increased spiking probability in response to echoes arriving from objects in 3D egocentric space; pre-vocal-motor neurons that fired before sonar call production; and sensorimotor neurons that exhibited pre-vocal-motor activity before sonar call onset and responded to the arrival of echoes. Our data also show that the bat's sonar vocal production

patterns can dynamically alter the tuning properties of neurons. These results demonstrate dynamic changes in midbrain neural activity in an animal moving naturally through space, interacting with objects along its path.

Disclosures: M.J. Wohlgemuth: None. **N.B. Kothari:** None. **C.F. Moss:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.01/RR6

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: CIHR
Réseau québécois de recherche sur le vieillissement

Title: Assessment of vascular amyloid pathology in brain microvessels isolated from persons with mild cognitive impairment or Alzheimer's disease

Authors: *P. BOURASSA[1], C. TREMBLAY[1], D. A. BENNETT[2], F. CALON[1]
[1]Ctr. De Recherche Du CHU De Québec, Quebec, QC, Canada; [2]Rush Alzheimer's Dis. Center, Rush Univ. Med. Ctr., Chicago, IL

Abstract: Compelling pieces of evidence suggest that blood-brain barrier (BBB) dysfunction is implicated in the pathophysiology of Alzheimer's disease (AD). Cerebral amyloid angiopathy (CAA), faulty Aβ peptide clearance and pericyte deficiency are all suspected to contribute to BBB dysfunction. Brain microvessels are typically investigated using immunostaining approaches on brain sections, with often limited possibilities for quantification. In this study, we sought to evaluate vascular amyloid pathology and pericyte loss in microvessels isolated from human parietal cortex samples (n= 60) from participants of the Religious Orders Study, a longitudinal clinical-pathological cohort study on aging and AD. We first validated human microvessel-enriched extracts (HME) generated from frozen tissue by Western blot and immunofluorescence experiments. We confirmed the enrichment of endothelial markers (claudin5 and occludin), and basal lamina marker (collagen IV) in the vascular fraction while neuronal markers were more abundant in the post-vascular fraction. To assess vascular amyloid pathology, ELISA showed that Aβ40 and Aβ42 levels in HME were increased in subjects with a neuropathological diagnosis of AD (+100% for Aβ40 and +200% for Aβ42, versus controls subjects), in ApoE4 carriers (+150% for both Aβ40 and Aβ42, versus ApoE4 non carriers) and in those with moderate to severe CAA (+400% for Aβ40 and +100% for Aβ42, versus individuals without CAA). In addition, Aβ40 and Aβ42 levels in HME were negatively correlated with ante mortem visuospatial ability, but not with global cognitive score. Western blot analyses showed that ABCB1 (p-glycoprotein) levels were reduced in AD subjects (-50%), positively correlated to

cognitive function and inversely correlated with Aβ40, but not with Aβ42. In contrast, apoE and β-secretase (BACE1) were increased in AD subjects, associated negatively with cognitive function and positively with Aβ40 and Aβ42 levels. Measurements of PDFGR-β and CD13, also called ANPEP, levels in HME by Western blot showed that both pericyte markers were reduced in individuals diagnosed with AD. Linear regression analyses showed that pericyte markers were correlated positively with cognitive scores and inversely with Aβ peptides concentrations. Overall, our data show that microvessel-enriched extracts generated from frozen human brain samples can be used to selectively analyze BBB cells and vascular Aβ pathology in the cerebrovasculature.

Disclosures: P. Bourassa: None. **C. Tremblay:** None. **D.A. Bennett:** None. **F. Calon:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.02/RR7

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: JST-CREST

Title: Identification of novel internalized cell surface proteins in human brain capillary endothelial cells by SWATH-MS

Authors: *S. ITO[1,2], M. OISHI[2], T. MASUDA[1,2], T. FURIHATA[3], S. OHTSUKI[1,2]
[1]Fac. of Life Sci., [2]Sch. of Pharm., Kumamoto Univ., Kumamoto, Japan; [3]Grad. Sch. of Med., Chiba Univ., Chiba, Japan

Abstract: The blood-brain barrier (BBB) regulates and restricts the transport of therapeutic drugs, antibodies, and nanoparticles that are used to treat central nervous system (CNS) disorders. Drug delivery to the brain still remains one of the major challenges that needs to be overcome. Efficient receptor-mediated transcytosis (RMT) across the BBB is an important strategy for drug delivery to the CNS. Although the transferrin receptor (TFR) is a promising molecule within the brain-targeted drug delivery system, concerns regarding its safety limits its application in humans. Thus, the purpose of the present study was to identify novel cell surface proteins that are selectively expressed and internalized into human brain capillary endothelial cells in vitro in order to identify novel RMT molecules at the BBB. To find BBB-selective RMT molecules, we used the hCMEC/D3 and HBMEC/ciB cell lines as BBB model and HUVEC as a peripheral blood vessel model. The proteins expressed in the plasma membrane of the cells were biotinylated with or without EZ-Link NHS-Biotin solution in PBS for 30 min at 4°C (cell surface fraction), and then treated with 20% human serum in PBS for 5 min at 37°C. To remove biotin from the biotin-labeled residual surface proteins, the cells were washed with or without a

MESNA wash buffer (internalized fraction). Biotinylated proteins in the samples were captured using streptavidin-immobilized magnetic beads. The biotinylated proteins were then eluted from the beads using DTT in PTS buffer. Silver staining showed that biotinylated proteins were detected in the cell surface and internalized fractions. Using SWATH-MS analysis, 563 hCMEC/D3, 314 HBMEC/ciB, and 399 HUVEC proteins were identified in the cell surface fractions. In the plasma membrane, approximately 378 hCMEC/D3 (57%), 197 HBMEC/ciB (63%), and 225 HUVEC (64%) biotinylated proteins were expressed after excluding the cytosolic proteins annotated via Gene Ontology analysis. Furthermore, 109 hCMEC/D3, 28 HBMEC/ciB, and 85 HUVEC internalized cell surface proteins were extracted using our original criteria. Among these, 73 proteins were BBB-selective internalized proteins. Considering the expression levels of these proteins in the isolated hCMEC/D3 plasma membrane fraction using SWATH-MS, 20 proteins (including TFR) were speculated to be candidate molecules for RMT at the BBB. These results suggest that we identified proteins internalized into human brain capillary endothelial cells in vitro using a cell surface biotinylation-based internalization method. Our present study provides novel information regarding the development of a BBB-permeable, brain-targeted drug delivery system.

Disclosures: S. Ito: None. **M. Oishi:** None. **T. Masuda:** None. **T. Furihata:** None. **S. Ohtsuki:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.03/RR8

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: N.I.H. 5 R01-DA11271-
NIH/NINDS 1R01NS099292-01A1

Title: Blood-brain barrier: Pilot investigations on regional distribution of sodium-hydrogen exchanger and tight junction protein expression after cortical kcl injection

Authors: *J. KIM[1], K. COTTIER[2], E. GALLOWAY[2], T. VANDERAH[2], T. DAVIS[2], T. LARGENT-MILNES[2]
[1]Neurosci., [2]Univ. of Arizona, Tucson, AZ

Abstract: Progressive research in pharmacology and neurology has recently centered around the molecular constituents of the blood-brain barrier (BBB) whose restrictive properties are required information for development of effective treatments for neurological disorders such as migraine headaches. Recent studies show implication of the membrane solute carrier Na+/H+ exchanger (NHE) in migraine physiology. Clinical studies show a tripled rate of migraine onsets in women

over men in America and an approximately doubled rate worldwide, indicating sex hormones as a regulator of NHE expression and function. To determine the integrity of the BBB in migraine with aura models, expression of the tight junction proteins known to hold the BBB intact were probed for. We carried our experiment via molecular and behavioral techniques utilizing rat models grouped by gender and treatment. Our investigations targeted the sodium/hydrogen exchanger 1 (NHE1) isoform of NHE and the tight junction proteins Occludin, Claudin-5 and Zonula occludens-1. Our three areas of interests were the brain and brainstem in the CNS and the trigeminal nerve in the PNS. Funded by Provost and a grant from the Arizona Area Health Education Centers (AHEC) Program. The content is solely the responsibility of the authors and does not necessarily represent the official views of Arizona AHEC.

Disclosures: K. Cottier: None. **E. Galloway:** None. **T. Vanderah:** None. **T. Davis:** None. **T. Largent-Milnes:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.04/RR9

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: the Sasakawa Research Grant for Young Scientists 2018-4053

Title: The effect of circulating angiotensin II on blood-brain barrier vascular permeability in the hippocampus of normotensive rats

Authors: *S. HAMASAKI, T. MUKUDA, Y. KOYAMA, T. KAIDOH
Tottori Univ., Yonago, Japan

Abstract: Blood proteins such as hormones cannot penetrate from systemic circulation into the brain including the hippocampus, owing to the presence of the blood−brain barrier (BBB). However, hypertensive model rats show an increased BBB permeability, in which angiotensin II (Ang II) participates in its regulation mechanisms. In contrast, effect of Ang II on BBB permeability in normotensive rats has not yet been examined. We inspected effects of physiological oscillation of circulating Ang II on BBB permeability in normotensive rats. To induce a transient elevation of circulating Ang II within the physiological ranges, rats were deprived of water for 16 hours per day during a 7-day experimental period. To detect BBB permeability histologically, rats were injected intravenously with a fluorescent dye, Evans blue (EB), which cannot cross the BBB, 15 min before transcardiac perfusion for fixation on the last day of the experimental period. EB is often used to evaluate an increased BBB permeability in the brain by detecting its extravasation into the parenchyma histologically and biochemically. In this study, we adopted a novel histological methodology for highly sensitive detection of EB; we

found that hippocampal neurons take up EB, presumably through endocytosis, and accumulate it in the somata even when the extravasation of the dye was difficult to detect. Using this technique, we can quantify BBB permeability by counting neurons stained with EB in the brain. Unexpectedly, EB-positive neurons were found in the hippocampal dentate gyrus in controls, suggesting a constitutively increased BBB permeability in the hippocampus. Moreover, the number of EB-positive neurons in the water−deprived rats increased compared with that in controls. This result suggest a possibility that a transient elevation of circulating Ang II induced by water deprivation increases BBB permeability in the hippocampal dentate gyrus of the normotensive rats. To determine the types of neurons stained with EB, immunostaining for several neurochemicals including a marker protein for the interneuron, parvalbumin, was made. Some EB-positive neurons (>15 μm) localized in the hilus of the dentate gyrus were immunoreactive for parvalbumin, indicating that these are interneurons. Taken together, an increased BBB permeability induced by Ang II would not only increase opportunities for circulating proteins to contact neurons, such as interneurons, in the hippocamapl dentate gyrus, and but also modulate neuronal activities.

Disclosures: S. Hamasaki: None. **T. Mukuda:** None. **Y. Koyama:** None. **T. Kaidoh:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.05/RR10

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: AMED-CREST

Title: Association between blood-brain barrier transport system alterations and brain parenchymal abnormalities in a mouse model of diet-induced insulin resistance assessed using quantitative proteomics

Authors: *S. OGATA[1], S. ITO[1,2,3], T. MASUDA[1,2,3], S. OHTSUKI[1,2,3]
[1]Grad. Sch. of Pharmaceut. Sci., [2]Fac. of Life Sci., Kumamoto Univ., Kumamoto, Japan; [3]AMED-CREST, Tokyo, Japan

Abstract: The blood-brain barrier (BBB) transport system plays a key role in the maintenance of brain parenchymal functions. Insulin resistance has been reported to contribute to BBB breakdown, the details of which are important for understanding the development of dementia because insulin resistance in type 2 diabetes mellitus is a risk factor for dementia, including Alzheimer's disease and vascular dementia. The purpose of the present study was to investigate the association between BBB transport system alterations and brain parenchymal abnormalities in a mouse model of diet-induced insulin resistance using quantitative proteomics. A high-fat

diet (HFD) was fed for 2 or 10 weeks to 8-week-old mice, which exhibited mild or severe insulin resistance, respectively. The expression levels of BBB transporters [Glut1 (39%), Mdr1 (36%)] and tight junction proteins [claudin-5 (53%), occludin (36%)] were significantly reduced in the brain capillary-rich fraction (Bcap) of 2-week HFD-fed mice, but these were not altered in that of 10-week HFD-fed mice. The expression of Mct1 protein was increased 2.4-fold in the Bcap of 10-week HFD-fed mice, but this was not altered in that of 2-week HFD-fed mice. In 2-week HFD-fed mice, immunohistochemical analysis showed no reduction of brain capillary density but a reduction in Glut1 and Mdr1 protein expression, similar to that measured by SWATH-MS. In addition, functional analysis showed reduced Glut1 and Mdr1 activity in 2-week HFD-fed mice. In the cerebral cortex of these mice, the expression of neurofilament-L (38%) and -M (29%) was significantly reduced. In the hippocampus, neurofilament-L (32%), -M (34%), -H (25%), and CaMKII (31-38%) levels were significantly reduced in 2-week HFD-fed mice. No significant reduction of neurofilament-L, -M, -H, or CaMKII levels was observed in the cerebral cortex and hippocampus of 10-week HFD-fed mice. The association analysis revealed that the changes of Glut1 and Mdr1 protein expression were closely related with that of neurofilament and CaMKII in both 2- and 10-week HFD-fed mice. The present results suggest that mild insulin resistance causes BBB transport system breakdown in the early phase of type 2 diabetes mellitus. This alteration in the brain may trigger the development of cognitive dysfunction.

Disclosures: S. Ogata: None. **S. Ito:** None. **T. Masuda:** None. **S. Ohtsuki:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.06/RR11

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Lundbeck Foundation grant
Danish Medical Research Council grant
NOVO-Nordisk foundation grant

Title: Contributions of the glycocalyx, endothelium, and extravascular compartment to the blood-brain barrier

Authors: *N. KUTUZOV[1], H. FLYVBJERG[2], M. LAURITZEN[1]
[1]Univ. of Copenhagen, Kobenhavn N, Denmark; [2]Tech. Univ. of Denmark, Copenhagen, Denmark

Abstract: Drug design for brain delivery usually focuses on the drug's ability to cross the vascular endothelium of the blood-brain barrier; thus, the glycocalyx and the astrocyte endfeet remain under-studied. We employed two-photon microscopy of single cortical capillaries to

record the passive transport of sodium fluorescein and fluorescently labelled dextran from the blood into the brain in anesthetized mice. We found that fluorescein penetrated nearly the entire glycocalyx volume, but dextran penetrated less than 50% of the volume. We found that the extravascular compartment, a region outside the vessel, which colocalizes with astrocyte endfeet, restricted passive transport of the two fluorescent dyes. The diffusion coefficients of the dyes were an order of magnitude lower in the perivascular compartment than in the brain parenchyma. Finally, we formulated a transport model to estimate the permeability of the healthy and the mannitol-disrupted blood-brain barrier. Our results suggested that the blood-brain distribution of small and large hydrophilic molecules was determined by three separate barriers: the glycocalyx, the endothelium, and the perivascular compartment.

Disclosures: N. Kutuzov: None. **H. Flyvbjerg:** None. **M. Lauritzen:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.07/RR12

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: AMED-CREST

Title: Transport activity impairment of creatine transporter (G561R), a novel mutation associated with creatine transporter deficiency, by abnormal N-glycosylation and cellular locaization

Authors: *T. UEMURA[1], S. ITO[1,2,3], T. MASUDA[1,2,3], Y. OTA[4], M. TACHIKAWA[4], T. WADA[5], M. HIRAYAMA[1,2,3], T. TERASAKI[4], S. OHTSUKI[1,2,3]
[1]Grad. Sch. of Pharmaceut. Sci., [2]Fac. of Life Sci., Kumamoto Univ., Kumamoto, Japan; [3]AMED-CREST, Tokyo, Japan; [4]Grad. Sch. of Pharmaceut. Sci., Tohoku Univ., Sendai, Japan; [5]Grad. Sch. of Med. Sci., Kyoto Univ., Kyoto, Japan

Abstract: Creatine transporter deficiency (CRTD) is the second-most common cause of X-linked intellectual disability, and caused by loss-of-function mutations in the creatine transporter (CRT) gene (*SLC6A8*). We previously reported that CRT majorly contributes to supplying creatine to the brain across the blood-brain barrier (BBB), in rodents. We also reported a novel CRT gene missense mutation (c.1681G>C, Gly561Arg) in Japanese CRTD patients, who had low cerebral creatine levels. However, the mechanism by which G561R-CRT mutation causes a reduction in cerebral creatine levels remains unclear. The purpose of the present study was to clarify the contribution of CRT to creatine transport across the human BBB *in vitro* and the mechanism of functional attenuation of G561R-CRT. Quantitative proteomics showed that the CRT protein was expressed in the plasma membrane of the human brain endothelial cell line

(hCMEC/D3) as a human BBB model. [^{14}C]creatine uptake by hCMEC/D3 cells was decreased by unlabeled creatine, a specific CRT inhibitor (β-guanidinopropionic acid), and CRT-targeted siRNAs. The uptake analysis also revealed that G561R-CRT mutation reduced the [^{14}C]creatine uptake by the skin fibroblasts, which are derived from patients harboring the G561R-CRT mutation, and by G561R-CRT expressing 293 cells. Immunohistochemical analysis showed that G561R- CRT protein was localized in the intracellular compartment, while the wild-type CRT (WT-CRT) protein was predominantly localized at the plasma membrane of 293 cells. Western blot analysis revealed that WT-CRT protein was detected at 68 kDa in the plasma membrane fraction of WT-CRT expressing 293 cells, whereas G561R-CRT protein was predominantly detected at 55 kDa in the crude membrane fraction of G561R-CRT expressing 293 cells. Both bands shifted to 50 kDa following treatment with N-glycosidase. These results suggest that functional attenuation of G561R-CRT mutation was caused by defective protein trafficking to the plasma membrane, due to protein misfolding and altered N-glycosylation. As a result, G561R-CRT mutation causes to impair creatine supply into CNS across the human BBB.

Disclosures: T. Uemura: None. **S. Ito:** None. **T. Masuda:** None. **Y. Ota:** None. **M. Tachikawa:** None. **T. Wada:** None. **M. Hirayama:** None. **T. Terasaki:** None. **S. Ohtsuki:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.08/DP09/RR13

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Lundbeck Foundation (Research Initiative on Brain Barriers and Drug Delivery; RIBBDD)

Title: Two-photon fluorescence imaging *in vivo* as a platform to investigate cell-penetrating peptides and liposome-based nanocarriers for drug delivery across the blood-brain barrier

Authors: *K. KUCHARZ[1], M. KRISTENSEN[2], K. KRISTENSEN[3], M. LUND[3], T. ANDRESEN[3], B. BRODIN[2], M. LAURITZEN[1,4]
[1]Inst. of Neurosci., [2]Dept. of Pharm., Univ. of Copenhagen, Copenhagen, Denmark; [3]Dept. of Micro- and Nanotechnology, Tech. Univ. of Denmark, Copenhagen, Denmark; [4]Glostrup Hosp., Copenhagen, Denmark

Abstract: INTRODUCTION: Successful development of new trans-BBB drug delivery systems to the brain relies on the feedback from *in vitro* models. These, however, do not represent the full extent of the complexity of the brain with all its structural and functional constituents, e.g. blood flow, glycocalyx or perivascular space. Furthermore, the properties of the

BBB differ in distinct regions of the vascular tree (i.e. in pial, penetrating, pre- and capillary vessels). The assessments *in vivo* are sparse and often limited to post-mortem evaluation or to crude brain imaging that lacks spatio-temporal resolution to resolve the fate of tested compounds at the BBB interface. Consequently, even promising carrier candidates fail in *in vivo* trials.
METHODS: Here, we used two-photon microscopy in living mice to characterize two distinct trans-BBB drug delivery approaches: (a) Tat cell-penetrating peptide (CPP) delivery system currently employed in clinical trials and (b) fluorescently labeled antibody-conjugated (i.e. targeted) liposome nanocarriers. The imaging data was supplemented with concurrent real-time functional readout of *in vivo* electrophysiology, i.e. systemic blood pressure, exhaled CO2 and neuronal activity.
RESULTS: We show that
a) Fluorescently labeled Tat successfully penetrates the BBB and accumulates in the brain, with slower kinetics of accumulation and clearance of the compound from the blood when conjugated to a therapeutic drug. However, regardless of cargo presence a significant fraction of Tat becomes trapped within specific elements of the BBB, i.e. endothelium in pial and penetrating arteries and in pericytes at the level of precapillary vessels and capillaries.
b) We formulated a novel class of fluorescently labeled endothelial transferrin receptor antibody-conjugated liposomes to track a single carrier nanoparticle at the BBB interface in the living brain. We show that targeted liposome nanocarriers associate over time at the BBB interface, primarily in pre- and capillary vessels, where they exhibit limited lateral motility. Although more stable in the blood than Tat-based compounds, a small fraction of liposomes becomes partially scavenged by circulating leukocytes.
SUMMARY: Understanding how drug delivery systems interact with the BBB, whether these interactions differ within the vascular tree, and characterizing dynamic properties of these interactions is of vital importance for development of novel drug delivery systems to the brain. High spatio-temporal resolution two-photon imaging *in vivo* may be instrumental for optimization of existing approaches and may help to identify new strategies for trans-BBB drug delivery *in vivo*.

Disclosures: K. Kucharz: None. **M. Kristensen:** None. **K. Kristensen:** None. **M. Lund:** None. **T. Andresen:** None. **B. Brodin:** None. **M. Lauritzen:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.09/RR14

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: Single-domain antibody against insulin-like growth factor-1 receptor (IGF1R) undergoes receptor-mediated transcytosis and delivers pharmacologically efficacious levels of pain-suppressing neuropeptide galanin across the blood-brain barrier

Authors: *W. ALATA, A. YOGI, E. BRUNETTE, U. IQBAL, K. KEMMERICH, M. MORENO, D. STANIMIROVIC
Natl. Res. Council (NRC), Ottawa, ON, Canada

Abstract: The blood-brain barrier (BBB) is one of the biggest challenges for the treatment of neurological diseases, as the majority of biologics do not cross the BBB sufficiently to achieve a pharmacological response. Therefore, it is crucial to develop new delivering technologies suited for delivery of biologics. This can be achieved using receptor-mediated transcytosis pathways that physiologically deliver large molecules across the BBB. In this study, a single domain antibody raised against the extracellular domain of the human insulin-like growth factor-1 receptor (IGF1R) by llama immunization (IGF1R4 V_HH) was evaluated for its: i) ability to transmigrate across an *in vitro* rat BBB model, ii) *in vivo* brain uptake by fluorescence- based *in situ* brain perfusion technique (ISBP), iii) ability to deliver galanin (Gal, non-crossing BBB analgesic neuropeptide) to the brain and induce a central pharmacological response. In contrast to negative control V_HH A20.1, IGF1R4 V_HH antibody showed a saturable BBB transcytosis *in vitro*. ISBP demonstrated that mice perfused with 500 µg of fluorolabeled IGF1R4-Fc-CF790 exhibited a significantly higher total brain fluorescence intensity ($p < 0.05$) and increased distribution volume (Vd, ~4-fold, $p < 0.01$) compared to those perfused with A20.1-Fc-CF790. Brain perfusion with increasing doses of IGF1R4-Fc-CF790 (50 – 800 µg) resulted in a linear accumulation plateauing at approximately 400 µg (~ 1 µM), confirming a saturable mechanism of transport. To evaluate the ability of IGF1R4 V_HH to deliver a drug payload into the brain, IGF1R4 chemically conjugated to Gal (IGF1R4-Gal) was tested in a Hargreaves model of inflammatory pain. As expected, iv injection of Gal alone did not result in any analgesic effect as it does not cross the BBB. In contrast, animals injected with equimolar concentration of IGF1R4-Gal (7 mg/kg) showed a potent suppression of thermal hyperalgesia. A repeated dose (7mg/kg) of IGF1R4-Gal 1 h after the first injection failed to induce additional analgesic effect; however, the analgesic response was recovered when IGF1R4-Gal was injected 24 h post-first injection. Similarly, the brain uptake of IGF1R4-Fc-CF790 perfused 1 h after injection of 7 mg/kg IGF1R4 V_HH was reduced by~ 27% compared to that in saline injected animals; however, the brain uptake was recovered 24 h post injection of IGF1R4 V_HH, suggesting reduced IGF1R capacity to engage new antibody molecules (due to down-regulation or rate of recycling) for a period of time between 1h-24h. In conclusion, IGF1R4 V_HH is a novel single domain antibody targeting IGF1R that shows receptor-mediated transport and ability to deliver pharmacological cargo across the BBB.

Disclosures: W. Alata: None. **A. Yogi:** None. **E. Brunette:** None. **U. Iqbal:** None. **K. Kemmerich:** None. **M. Moreno:** None. **D. Stanimirovic:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.10/SS1

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: American Heart Association Grant 17SDG33410777
NIH Grant 2P01HL095070

Title: Poldip2 depletion blocks COX-2 expression and protects against LPS-induced blood-brain barrier disruption

Authors: D. KIKUCHI[1], A. CAMPOS[3], R. SADIKOT[2], B. LASSÈGUE[1], K. GRIENDLING[1], *M. S. HERNANDES[1]
[1]Cardiol., [2]Pulmonary and Critical Care, Emory Univ., Atlanta, GA; [3]Neurosci., Hosp. Sírio-Libanês, Sao Paulo, Brazil

Abstract: Introduction:
Sepsis is a systemic inflammatory response characterized by endothelial permeability which can be modeled by lipopolysaccharide (LPS). Septic encephalopathy (SE) is a frequent complication of sepsis and a major factor in sepsis mortality and morbidity. The blood-brain barrier (BBB) is compromised in SE, however, the signaling pathways that underlie this disruption require further study. Nuclear factor-κB (NF-κB) modulates the expression of proinflammatory mediators involved in sepsis, including cyclooxygenase-2 (COX-2). COX-2 catalyzes the first committed step of prostaglandin synthesis. In the brain, prostaglandin E2 (PGE2) induces endothelial permeability and facilitates BBB disruption. Polymerase δ-interacting protein 2 (Poldip2) depletion has previously been reported to abrogate BBB disruption following ischemic stroke. Here we investigated Poldip2 as a novel regulator of COX-2 and its downstream signaling.
Methods:
Intraperitoneal injection of LPS (18 mg/kg) was used to induce BBB disruption in Poldip2$^{+/-}$ and Poldip2$^{+/+}$ mice. BBB disruption was assessed by Evans blue extravasation 18 hours after LPS administration and measured spectrophotometrically after formamide extraction of the dye from whole brains. The cerebral cortices of Poldip2$^{+/+}$ and Poldip2$^{+/-}$ mice were isolated 6 hours after LPS injection and expression of inflammatory markers was evaluated by immunoblotting and ELISA. Primary rat brain microvascular endothelial cells were used to investigate the effect of Poldip2 depletion by siRNA on LPS-mediated COX-2 induction and adenovirus was used to study the effect of Poldip2 overexpression on COX-2 expression.
Results:
LPS induced BBB disruption in Poldip2$^{+/+}$ mice (Evans blue: 18±4 μM/g vs. 168±42 μM/g, $p<0.001$). BBB permeability was reduced in Poldip2$^{+/-}$ compared to Poldip2$^{+/+}$ mice 18 hours

after LPS injection (67±13 μM/g vs. 168±42 μM/g, $p<0.05$). In Poldip2$^{+/+}$ cortices, Poldip2, COX-2, and NF-κB expression was upregulated (45%, $p<0.05$, 79%, $p<0.01$ and 33%, $p<0.05$, respectively) after 6 hours of LPS. No induction was observed in Poldip2$^{+/-}$ mice, which had lower levels of COX-2 ($p<0.05$), NF-κB ($p<0.01$) and PGE2 (3744± 834 pg/mL vs. 6173± 488 pg/mL, $p<0.05$) than Poldip2$^{+/+}$ after LPS treatment. Consistent with our in vivo findings, depletion of Poldip2 blocked LPS-mediated COX-2 induction in cultured cells (n=2) and overexpression of Poldip2 induced COX-2 expression (n=1).

Conclusions:

Our data suggest that Poldip2 induces COX-2 and PGE2, thus mediating LPS-induced BBB disruption.

Disclosures: D. Kikuchi: None. **A. Campos:** None. **R. Sadikot:** None. **B. Lassègue:** None. **K. Griendling:** None. **M.S. Hernandes:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.11/SS2

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01 NS077678
NIH/NIEHS Grant R01 ES016931
NIH/NIEHS Grant R01 ES010563

Title: A novel human cell based model for evaluating brain iron uptake of pharmaceutical compounds and ferritin

Authors: B. CHIOU[1], E. NEAL[2], A. B. BOWMAN[3], E. LIPPMANN[2], I. A. SIMPSON[4], *J. R. CONNOR[1]
[1]Neurosurg., Penn State Col. of Med., Hershey, PA; [2]Chem. and Biomolecular Engin., Vanderbilt Univ., Nashville, TN; [3]Pediatric Neurol. Res. Lab., Vanderbilt Univ. MC, Nashville, TN; [4]Penn State Univ. Col. of Med., Hershey, PA

Abstract: Iron delivery to the brain is essential for multiple neurological processes such as myelination, neurotransmitter synthesis and, as it is for all organs, critical for the utilization of oxygen for energy production. Consequently, factors that influence iron transport across the blood brain barrier (BBB) can significantly impact neurological function. Understanding the mechanism by which iron transport across the BBB is regulated is crucial in developing treatments for brain iron deficiency. Using a novel model comprised of human BBB endothelial cells differentiated from induced pluripotent stem cells, we demonstrate the ability for apo-transferrin, holo-transferrin, hepcidin, and DMT1 to impact iron transport across the BBB.

Furthermore, we demonstrate that release of iron from the endothelial cells is similarly impacted by these proteins. Our model further shows a novel function for H-ferritin to transport iron across the BBB by binding to the T-cell immunoglobulin and mucin receptor 1 (Tim-1). We also provide evidence for a novel function of endothelial cells to synthesize and secrete transferrin and H-ferritin, providing another layer of regulation. As a clinical correlate, we also examine 5 pharmaceutical iron formulations given intravenously during clinical treatment of iron deficiency for their ability to cross the BBB. We report that, compared to the positive controls of transferrin and H-ferritin, the pharmaceutical iron formulations do not cross the BBB or significantly load the endothelial cells with iron. Finally, given the novelty of ferritin transport of iron, we provide in vivo evidence for ferritin as an iron transport protein and demonstrate a sex and genotype effect on uptake during development. Our data demonstrate the ability for the brain to modulate and exert exquisite control over iron transport and identifies ferritin as a novel and potent iron delivery protein.

Disclosures: B. Chiou: None. **E. Neal:** None. **A.B. Bowman:** None. **E. Lippmann:** None. **I.A. Simpson:** None. **J.R. Connor:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sidero Bioscience.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.12/SS3

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: A human stem cell derived blood brain barrier model that provides a translational method to predict adeno-associated virus barrier penetration for therapeutic gene delivery to the brain

Authors: *T. P. GRAY
Translastional Biol., Biogen, Cambridge, MA

Abstract: Adeno-associated virus (AAV) serotype 9 has recently emerged as capsid featuring enhanced blood-brain barrier (BBB) penetration, making it an attractive gene-therapy vehicle to treat neurodegenerative diseases. Based on a recent publication (Merkel et. al J Neurochem), it is a serotype-specific characteristic, as it has been shown that AAV2 does not transport, but transduces the BBB. Of note, to date the AAV9 derivative PHP.B (described in Deverman et al. Nat Biotech 2016) has only demonstrated enhanced penetration in the C57BL6 mouse strain. To resolve the gap of interspecies translation we have designed a ‘human-first’ approach to examine the potential of different AAV serotype candidates for gene delivery across a transwell in vitro BBB model.
Using an array of primary, immortalized, and induced pluripotent stem cell (iPSC)-derived brain microvascular endothelial cells (BMEC) from various species, we have optimized BBB transwell

models for a variety of functional assays, including validation and characterization of AAV serotype-specific penetration, transduction, and species translatability. Human iPSC-derived BMECs are an ideal choice for BBB modeling due to their adult human origin and ability for bulk production to ensure reproducibility. The iPSC-BMECs produced from our optimized differentiation, dissociation and sub-culture conditions (protocol based off Lippmann et al. Nat Biotech 2012) display relevant BBB surface markers including CD31, Glut-1, ZO-1, and occludin. Notably, for iPSC-BMEC in monoculture, we demonstrate transendothelial electrical resistance (TEER) values up to 4000 $\Omega*cm^2$ and extend the functional assay window by sustaining $\geq$1000 $\Omega*cm^2$ TEER for a week post dissociation, significantly above our cutoff of 500 $\Omega*cm^2$ for functional assays to ensure no passive diffusion of large molecules and AAV across the BBB.
We have started validating our BBB models with AAV2, AAV9, and PHP.B loaded with a fluorescent payload and found serotypes to behave differently in transcytosis and transduction, of both endothelial cells and human iPSC-derived neurons cultured in the basolateral compartment. Importantly, the latter demonstrates that capsids that have undergone transendothelial transcytosis are still fully functional and able to transduce cells "behind the BBB". We conclude that our model shows potential to be an efficient way to predict which serotypes and engineered capsid modifications may improve endothelial cell barrier penetrance, transduction, and facilitate the translation between animal models and human, altogether holding promise to increase the probability of success in gene therapy research and development.

Disclosures: T.P. Gray: None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.13/SS4

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Wisconsin Alumni Research Foundation
University of Wisconsin-Madison School of Pharmacy
Michael J Fox Foundation for Parkinson's Research

Title: Intranasal delivery of full-length immunoglobulin G antibodies to the central nervous system in APP/PS1 and non-transgenic mice: Feasibility, permeation enhancement and implications for Alzheimer's disease immunotherapy

Authors: *G. NEHRA[1], N. N. KUMAR[1], K. VANG[1], T. XIE[1], R. G. THORNE[1,2,3,4]
[1]Sch. of Pharm., [2]Clin. Neuroengineering Training Program, [3]The Ctr. for Neurosci. and Neurosci. Training Program, [4]Cell. and Mol. Pathology Grad. Program, Univ. of Wisconsin-Madison, Madison, WI

Abstract: The intranasal route can non-invasively deliver large macromolecules into the central nervous system (CNS), bypassing the blood-brain barrier, via olfactory and trigeminal nerve pathways that exist in the nasal mucosae (Thorne et al. *Neuroscience.* 2004; Lochhead & Thorne. *Adv Drug Deliv Rev.* 2012). Further widespread distribution occurs along perivascular spaces surrounding major cerebral blood vessels (Lochhead et al. *J Cereb Blood Flow Metab.* 2015). We have previously shown that intranasal delivery of immunoglobulin-G (IgG) can be enhanced by modulating nasal epithelial permeability with intranasal matrix metalloproteinase-9 (MMP-9) pre-treatment in rats. Here, we investigated this effect across species by intranasally administering non-targeted mouse IgG following MMP-9 pre-treatment in 7-10 month old, female APPswe/PS1dE9 and non-transgenic mice. We first quantified acute CNS distribution profiles for a tracer dose of ^{125}I-labeled IgG following saline pre-administration in anesthetized mice (n = 6), showing rapid CNS delivery within 30 minutes in non-transgenic as well as in APP/PS1 mice. Following pretreatment with activated mouse MMP-9 (100 nM; activity validated in-house using a fluorometric assay), we observed a trend for enhanced IgG exposure in multiple CNS regions (n = 6). Confocal imaging of sections obtained from APP/PS1 mice having intranasally administered AF594-labeled IgG following MMP-9 pre-treatment confirmed signal in the brain associated with a compartment adjacent to but not co-localizing with PECAM-1/CD31-positive endothelial cells, i.e. the perivascular space. IgG signal was also evident near insoluble plaques, suggesting the possibility of amyloid-antibody interactions if a targeted IgG were used. We have now initiated a chronic study with 4-month old, awake APP/PS1 mice involving intranasal delivery of a targeted-antibody against the beta-amyloid N-terminus (6E10) over 14 weeks; insoluble plaque burden and olfactory behavior differences will be compared across treatment groups. Overall, our findings offer insights into whether intranasal antibody delivery to the brain is viable and potentially modifiable in APP/PS1 mice. The results suggest the intranasal route may ultimately be useful for future Alzheimer's disease immunotherapy approaches.

Disclosures: G. Nehra: None. **N.N. Kumar:** None. **K. Vang:** None. **T. Xie:** None. **R.G. Thorne:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.14/SS5

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01AG023084
NIH Grant R01NS090904
NIH Grant R01NS034467
NIH Grant 1R01NS100459

Foundation Leducq Transatlantic Network
Zilkha Senior Scholar Support

Title: Hypoxia-induced vascular responses in the adult mouse brain

Authors: *M. D. SWEENEY, M. T. HUUSKONEN, A. MONTAGNE, C. MURPHY, K. KISLER, Z. ZHAO, B. ZLOKOVIC
Zilkha Neurogenetic Institute, Dept. of Physiol. and Neurosci., USC, Los Angeles, CA

Abstract: Mild continuous hypoxia is a phenomenon observed in several central nervous system (CNS) conditions including diabetic retinopathy, chronic hypoperfusion, and Alzheimer's disease (AD). Pericytes, mural cells that enwrap capillaries, become dysfunctional and degenerate in ischemic stroke, diabetic retinopathy and AD. Pericytes are vital orchestrators of key neurovascular functions including blood-brain barrier (BBB) integrity, cerebral blood flow (CBF), and angiogenesis. Increased CBF and angiogenesis are physiological responses in brain elicited by a mild hypoxic state. The transcriptional regulation of these structural/functional hypoxic responses has never before been investigated in the adult brain, nor has its corresponding impact on brain microvascular health. Adult mice exposed to mild continuous hypoxia up to 21 days show both an acute increase in capillary diameter and red blood cell velocity in the somatosensory cortex using longitudinal multiphoton imaging. Additionally, several imaging techniques reveal a progressively increased regional rate of microvascular density accompanied by transient BBB permeability. Moreover, RNA-sequencing analysis of brain microvascular pericytes and endothelial cells during different timepoints of mild continuous hypoxia reveals significant differentially expressed genes of pathways regulating angiogenesis (differentiation, proliferation, migration) and BBB permeability, determined via Ingenuity Pathway Analysis. Altogether, elucidating the transcriptional, structural and functional responses to mild continuous hypoxia in the adult brain is vital to inform therapeutic efforts to combat hypoxic insults and/or microvascular dysfunction in numerous CNS disorders.

Disclosures: M.D. Sweeney: None. **M.T. Huuskonen:** None. **A. Montagne:** None. **C. Murphy:** None. **K. Kisler:** None. **Z. Zhao:** None. **B. Zlokovic:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.15/SS6

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant NS100459
NIH Grant AG039452

Title: Pericyte ablation from the adult brain leads to acute disruption of the neurovascular unit

Authors: *B. V. ZLOKOVIC[1], A. M. NIKOLAKOPOULOU[2], K. KISLER[2], A. P. SAGARE[2], D. LAZIC[2], A. MONTAGNE[2], M. D. SWEENEY[2], Y. WANG[2], M. T. HUUSKONEN[2], Z. ZHAO[2]
[1]Zilkha Neurogenetic Inst., Keck Sch. of Med. of the Univ. of Southern California, Los Angeles, CA; [2]USC, Los Angeles, CA

Abstract: Brain pericytes are the vascular mural cells located within the basement membrane of blood microvessels. Pericytes maintain blood-brain barrier integrity, regulate cerebral blood flow (CBF) and participate in the clearance of brain toxic byproducts. Much of the knowledge has been gained from studies in mice with inherited pericyte deficiency caused by aberrant signaling between endothelial-derived platelet-derived-growth factor B (PDGF-B) and PDGF-receptor β (PDGFRβ) in pericytes. Here, we report the development of a new murine pericyte-specific Cre line using a double-promoter strategy and show Cre-dependent expression dtTomato reporter only in brain pericytes, but not in oligodendrocytes, oligodendrocyte progenitor cells, vascular smooth muscle cells, brain endothelial cells, astrocytes or microglia. Next, we developed a model with inducible pericyte ablation after diphtheria toxin (DT) administration in adult mice expressing the Cre-dependent human DT receptor (DTR) in pericytes. We show that acute ablation of pericytes leads to neurovascular dysfunction and a series of pathophysiological events that begin with dysregulated cerebral blood flow responses and blood-brain barrier breakdown causing rapid neuronal dysfunction and functional deficits. These data suggest that pericytes importantly keep the integrity of the neurovascular unit and that their loss leads to disruption of the neurovascular unit causing cerebrovascular disorder and white matter and neurodegenerative changes.

Disclosures: B.V. Zlokovic: None. **A.M. Nikolakopoulou:** None. **K. Kisler:** None. **A.P. Sagare:** None. **D. Lazic:** None. **A. Montagne:** None. **M.D. Sweeney:** None. **Y. Wang:** None. **M.T. Huuskonen:** None. **Z. Zhao:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.16/SS7

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: K99-R00 NS070920
R01 NS098273
F31 NS100565

Title: Acquisition of BBB properties by the developing brain vasculature is controlled by a retinoic acid-WNT signaling axis

Authors: *S. BONNEY, B. J. C. DENNISON, E. PETERMAN, M. WENDLANDT, J. A. SIEGENTHALER
Pediatrics, Univ. of Colorado Denver, Aurora, CO

Abstract: The formation of a functional blood-brain barrier (BBB) is crucial for the brain vasculature to properly support central nervous system (CNS) health. During development, endothelial cells that form the brain vasculature quickly obtain BBB properties which include the formation of tight junctions and recruitment of BBB support cells called pericytes. Acquisition of these BBB properties is required for vascular stability, thus understanding the developmental signals that regulate this process are important. Endothelial WNT signaling is a known driver of brain vascular development and BBB properties however it is unclear how endothelial WNT signaling is regulated. We recently showed that mouse embryos with disruptions in retinoic acid (RA) synthesis (*Rdh10* mutants) and endothelial RA signaling (*Pdgfbi*^{cre}; *dnRAR403*$^{fl/fl}$) have ectopic WNT signaling in the brain vasculature. Here we show that increased vascular WNT signaling in *Pdgfbi*^{cre}; *dnRAR403*$^{fl/fl}$ and *Rdh10* mutant embryos is associated with elevated expression of the WNT transcriptional effector, β-catenin, in the brain endothelium. These RA mutants also have increased numbers of pericytes along the brain vasculature. However the WNT-regulated tight junction protein, Claudin-5, appears unaltered. Using *in vitro* studies in brain endothelial cells, we show that RA may inhibit WNT signaling by targeting β-catenin for proteasomal degradation. Our data suggests that the inhibition of WNT signaling by RA is important for regulating pericyte recruitment during brain vascular development and this may be mediated through proteasomal degradation of β-catenin. In addition, we find that the downstream WNT target, Sox17, is required for pericyte recruitment to the developing brain vasculature, potentially by directly regulating the expression of the pericyte mitogen PDGFB. Our studies highlight the importance of regulating vascular WNT signaling by RA to ensure proper development of the BBB, most notably through pericyte recruitment. This inhibitory regulation of WNT signaling by RA could be needed to prevent over-recruitment of pericytes that might impair endothelial-pericyte interactions crucial for BBB formation and maintenance.

Disclosures: S. Bonney: None. **B.J.C. Dennison:** None. **E. Peterman:** None. **M. Wendlandt:** None. **J.A. Siegenthaler:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.17/SS8

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Lundbeck Foundation Research Initiative on Brain Barriers and Drug Delivery (RIBBDD)

Title: ApoM deficiency induces an increase in the BBB permeability via the sphingosine-1-phosphate signaling pathway *in vivo*

Authors: *M. M. JANIUREK[1], K. KUCHARZ[1], C. CHRISTOFFERSEN[3,2], L. NIELSEN[4], M. LAURITZEN[1,5]
[1]Dept. of Neurosci., [2]Dept. of Biomed. Sci., Univ. of Copenhagen, Copenhagen, Denmark; [3]Dept. of Clin. Biochem., Rigshospitalet, Copenhagen, Denmark; [4]The Fac. of Hlth., Aarhus Univ., Aarhus, Denmark; [5]Dept. of Clin. Neurophysiol., Rigshospitalet-Glostrup, Copenhagen, Denmark

Abstract: Introduction. Modulation of endogenous signaling pathways that regulate the blood-brain barrier (BBB) permeability represents a potential strategy for increased drug delivery to the brain. Sphingosine-1-phosphate receptors (S1PRs) are surface membrane receptors located on vascular endothelial cells. In a healthy organism, the majority of the S1PR agonist, i.e. sphingosine-1-phosphate (S1P), is transported in the blood by the molecular chaperone, apolipoprotein-M (ApoM), which is a critical part of HDL. Disruption of ApoM-S1P signaling is associated with a permeable endothelial barrier in the lungs. This led us to examine the role of S1P signaling for the BBB integrity.
Aim. To determine the importance of the S1P/S1PR signaling pathway for BBB integrity and function in ApoM knockout mice.
Methods. We used *in vivo*two-photon fluorescence microscopy in ApoM deficient ($ApoM^{-/-}$) mice and in wild-type litter-mates. To monitor BBB permeability in a living brain, water-soluble fluorophores of varying sizes were injected intravenously, and BBB integrity was assessed via a craniotomy over the somatosensory cortex. The accumulation of the fluorophores was measured in real time at cortical depths ranging from 0 to 120 μm relative to the brain surface. Furthermore, transmission electron microscopy (TEM) was applied for a quantitative ultrastructural analysis of the BBB.
Results. Loss of ApoM-mediated S1P transport led to increased permeability towards blood-circulating fluorescent molecules. Compared to wild-type litter-mates, the BBB in $ApoM^{-/-}$mice exhibited a 5-fold increase in the accumulation of small fluorophores (with MW less than 0.65kDa) within 30 minutes post injection. This effect was not observed with larger molecules. Moreover, pharmacological modulation of the S1P/S1PR pathway with an S1PR agonist led to reversal of the phenotype and partially reinstated the BBB integrity. Preliminary data from TEM show a difference in the morphology of the junctional complexes in $ApoM^{-/-}$ mice, with no difference in vesicular components of the endothelium. These results indicate that the loss of the ApoM-mediated S1P transport results in an increased paracellular permeability, while transcellular transport remains intact.
Conclusion. The BBB integrity towards blood circulating molecules can be altered by targeted modulation of the ApoM/S1P/S1PR signaling, implying that this pathway plays an important role in maintaining the integrity of the BBB. Disruption of ApoM/S1P/S1PR signaling may be a

novel method for bidirectional modulation of BBB integrity for increased trans-BBB drug delivery to the central nervous system.

Disclosures: M.M. Janiurek: None. **K. Kucharz:** None. **C. Christoffersen:** None. **L. Nielsen:** None. **M. Lauritzen:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.18/SS9

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Mary E. Groff Charitable Trust
Vickie and Jack Farber Institute for Neuroscience

Title: Sphenopalatine ganglion stimulation disrupts tight junction protein architecture and increases blood-brain barrier permeability

Authors: *R. F. SCHMIDT, M. J. LANG, G. P. STRICSEK, R. H. ROSENWASSER, A. D. SHARAN, L. IACOVITTI
Dept. of Neurosurg., Thomas Jefferson Univ., Philadelphia, PA

Abstract: Introduction: The sphenopalatine ganglion (SPG) provides parasympathetic innervation to the anterior intracranial circulation in mammals. Early investigations suggest that SPG stimulation increases blood-brain barrier (BBB) permeability. We demonstrate the effects of SPG stimulation on the BBB by quantifying fluorescent tracer extravasation into brain after specimen homogenization and present a putative mechanism of action by demonstrating disruption of tight junction proteins in stimulated rat brain. Methods: Female Sprague-Dawley rats (235-240g, n=8 rats) underwent intermittent SPG stimulation at 10Hz for 40 minutes with concurrent femoral vein injection of 70kDa FITC-dextran. Five 3mm sections from each cerebral hemisphere were obtained from each rat and homogenized in 7.5% trichloroacetic acid (n=80 specimens). Control rats (n=5 rats, 50 specimens) underwent tracer injection without SPG stimulation. Fluorescence uptake was calculated as the percentage of tracer concentration in the supernatant of homogenized brain to serum concentration. Tight junctions were evaluated in separate control (n=3) and stimulated rats (n=3) that did not undergo tracer injection. 20µm brain sections were fixed in 100% methanol and stained for rat endothelial cell antigen (RECA-1) and the tight junction proteins occludin or ZO-1. 20X images (n=120 each group) were obtained and the percent overlap of occludin or ZO-1 with RECA-1 was quantified using a computerized colocalization algorithm. Results: There was a 6-fold increase in fluorescence uptake in 10hz stimulated specimens compared to controls (0.28% vs 1.66%, t-test, &lt<0.0001). Additionally, there was a statistically significant decrease in the overlap of occludin and ZO-1 staining with

endothelium in stimulated rats (74.6% vs 39.7% and 67.1% vs 60.5%, respectively, &lt<0.0001 for both).Conclusions: Prolonged SPG stimulation at 10Hz increases BBB permeability, demonstrated by increased fluorescent tracer extravasation seen in homogenized rat brain specimens. Stimulation also appears to disrupt tight junction proteins, providing a possible mechanism for increased BBB permeability. Bypassing the BBB with SPG stimulation could open the door for new paradigms of therapeutic delivery for disorders of the CNS.

Disclosures: R.F. Schmidt: None. **M.J. Lang:** None. **G.P. Stricsek:** None. **R.H. Rosenwasser:** None. **A.D. Sharan:** None. **L. Iacovitti:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.19/SS10

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NHRI-EX107-10412NC

Title: Rapid and reversible disruption of the blood-brain barrier through carbogen inhalation

Authors: *K. LIAO[1,2], H.-L. WANG[2], V. C. WEI[2], T. W. LAI[1,2]
[1]China Med. Univ. Hosp., Taichung, Taiwan; [2]Gradaute Inst. of Clin. Med. Science, China Med. Univ., Taichung, Taiwan

Abstract: Carbogen was introduced nearly a century ago as a treatment for psychiatric disorders. We report here that carbogen induced BBB disruption indicated by extravasation of an intravenous protein tracer. When the tracer was injected immediately or 1-24 h post-carbogen inhalation, little or no detectable tracer was detected in the rat brains, suggesting the rapid reversibility of this response after carbogen exhalation. Despite marked BBB disruption, inhalation of carbogen for 30-90 min had no long-term effects on body weight, food intake, locomotor activity, or learning and memory performance. Our study introduced carbogen as a potential inhaled agent for BBB disruption.

Disclosures: K. Liao: None. **H. Wang:** None. **V.C. Wei:** None. **T.W. Lai:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.20/SS11

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: CIHR FRN 119312
NIH R01 EB003268

Title: Cellular response following focused ultrasound mediated blood-brain barrier opening: A two-photonmicroscopy study

Authors: *C. POON[1], K. HYNYNEN[2]
[1]Physical Sci., Sunnybrook Hlth. Sci. Ctr., Toronto, ON, Canada; [2]Med. Biophysics / Physical Sci., Univ. of Toronto / Sunnybrook Res. Inst., Toronto, ON, Canada

Abstract: Background: Focused ultrasound (FUS) is a non-invasive technique that can be used to deliver therapeutic agents, such as chemotherapeutics and stem cells, to targeted brain regions by temporarily opening the blood-brain barrier (BBB). Safety studies have shown that under controlled FUS parameters and with the addition of an ultrasound contrast agent, FUS can transiently open the BBB without causing erythrocyte extravasation. Two independent groups have provided evidence that FUS-mediated BBB opening itself, without the use of therapeutics, reduces Aβ plaque load and improves memory functions in mouse models of AD.
Rationale: The cellular response following FUS is currently unknown. An acute inflammatory response has been reported at six and 12 h following FUS. Transient inflammatory responses have been shown to promote Aβ plaque clearance and may be a mechanism by which FUS decreases Aβ plaque load.
Methods: To follow the cellular immune response following FUS-mediated BBB treatment, EGFP Wistar rats [Wistar-TgN(CAG-GFP)184Ys], which harbour GFP-positive leukocytes, were used in this study. A 5-mm craniotomy was prepared on the parietal bone for two-photon fluorescence microscopy. FUS was delivered using a ring transducer positioned over the craniotomy; increased BBB permeability was assessed by the leakage of a fluorescent dextran from the intra- to extravascular space. Cell identity was determined using immunohistochemistry.
Results: FUS treatment causes an activation of the neurovascular unit, leading to glial cell activation and recruitment of peripheral immune cells. Blood flow is also transiently affected.
Conclusion: FUS treatment to open the BBB is currently already in clinical trials for AD. However, much of the biological mechanisms behind its effects are unknown. These studies will determine the cell types involved and elucidate possible molecular pathways that are activated.

Disclosures: C. Poon: None. **K. Hynynen:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.21/SS12

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: CONACYT Grant No. 177594

Title: Monosodium glutamate-induced neonatally excitotoxicity modifies regionally the blood-brain barrier properties in the adult male rat

Authors: *B. F. FAJARDO-FREGOSO, J. L. CASTAÑEDA-CABRAL, C. BEAS-ZÁRATE, M. E. UREÑA-GUERRERO
Cell. and Mol. Biol., Univ. de Guadalajara (CUCBA), Zapopan, Mexico

Abstract: The Blood-Brain Barrier (BBB) is essential to maintain the central nervous system homeostasis. Plasmalemmal vesicle associated protein-1 (PV1) is considered a marker of BBB immaturity and claudin-5 is an essential component of the tight junctions. Several pathological states that course with excitotoxicity also show an increased vascular permeability in the acute phase, but it is unknown yet, if these changes are lasting. The goal of this work was to evaluate the long-term effects of monosodium glutamate (MSG)-induced neonatally excitotoxicity on BBB properties. Male newborn rats were randomly assigned to intact or MSG-treated group. MSG [4 g/kg of body weight (b.w.)] was subcutaneously administered at postnatal day (PD) 1,3,5 and 7. At PD60, the BBB permeability was evaluated through sodium fluorescein (2.5 ml/g of b.w. of 10% solution) penetrability to the motor cerebral cortex (MC), striatum, hippocampus, entorhinal cortex (EC) and hypothalamus in both normoosmolar and hyperosmolar conditions. Hyperosmolar condition was induced by 10 ml/kg of b.w. of 2.95 M NaCl solution intraperitoneally injected. The levels of protein expression of claudin-5 and PV1 were measured by western-blotting referred to β-actin in MC and hippocampus. Brain studied regions showed the followed fluorescein penetrability gradient: MC<striatum<hippocampus<EC<hypothalamus. No differences were found in normoosmolar condition between groups in any studied region. However, in hyperosmolar condition, fluorescein penetrability was higher in all regions of MSG-treated group, reaching a more significant change in the hypothalamus. The protein expression level of claudin-5 was decreased by MSG treatment, showing a marked decrease in the hippocampus. While PV1 displayed a slight increased expression level in the hippocampus of MSG-treated group. Results indicate that MSG-induced neonatally excitotoxicity has significant long-term effects on the BBB properties: 1) affecting the expression of structural proteins that are determinant in the barrier function, and 2) increasing its susceptibility to a hyperosmotic condition. Then our results suggest that the BBB is more susceptible to disrupt after an excitotoxic process, which it must be widely studied.

Disclosures: B.F. Fajardo-Fregoso: None. **J.L. Castañeda-Cabral:** None. **C. Beas-Zárate:** None. **M.E. Ureña-Guerrero:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.22/SS13

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: DGE-1650112
NIH R01 NS091281

Title: What are the molecular mechanisms of blood-brain barrier dysfunction in disease?

Authors: *C. P. PROFACI[1], K. BAJC[1], S. H. FU[1], J. P. MILLER[2], T. Z. ZHANG[1], R. DANEMAN[1]
[1]Univ. of California San Diego, La Jolla, CA; [2]Univeresity of California San Diego, La Jolla, CA

Abstract: The blood-brain barrier (BBB) is a set of properties unique to central nervous system (CNS) endothelial cells (ECs) that comprise the inner walls of blood vessels. In contrast to peripheral vessels, which allow extensive exchange of molecules and ions between the blood and tissue, CNS ECs exert tight control over what can enter the parenchyma. BBB dysfunction is a key component of many neurological conditions, including multiple sclerosis, stroke, epilepsy, and traumatic brain injury. Despite the vastly different triggers of these diseases, in each case vascular permeability causes an influx of blood-borne molecules, disruption of ionic homeostasis, and an increase in immune cell extravasation. These events contribute to the dysfunction, damage, and even degeneration of neurons, ultimately worsening clinical outcomes. Identifying common molecular changes in ECs during disease could point towards a therapeutic target for reducing BBB dysfunction in wide range of neurological diseases.
To investigate the molecular changes occurring in CNS endothelial cells during disease, we isolated endothelial cells from four disease models during BBB dysfunction and performed RNA sequencing. A set of 198 genes was upregulated across multiple conditions, suggesting a common pathway for BBB dysfunction regardless of the trigger of disease. To further probe this BBB dysfunction pathway, I took a two-pronged approach, investigating which other cell types might induce these endothelial changes as well as the mechanism by which these common transcriptional changes lead to BBB permeability.

Disclosures: C.P. Profaci: None. **K. Bajc:** None. **S.H. Fu:** None. **J.P. Miller:** None. **T.Z. Zhang:** None. **R. Daneman:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.23/SS14

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: University of Wisconsin-Madison School of Pharmacy
UW Institute for Clinical and Translational Research (NIH UL1TR000427 and KL2TR000428)
Wisconsin Alumni Research Foundation
National Science Foundation fellowship (DGE-1256259)

Title: Factors influencing therapeutic antisense oligonucleotide distribution in the CNS following intrathecal administration: Implications for neurodegenerative diseases

Authors: *B. WILKEN-RESMAN[1], M. E. PIZZO[1], R. G. THORNE[1,2,3,4]
[1]Div. of Pharmaceut. Sci., [2]Inst. for Clin. and Translational Res., [3]The Ctr. for Neurosci. and Neurosci. Training Program, [4]Cell and Mol. Pathology Grad. Program, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Antisense oligonucleotide (ASO) therapies administered intrathecally for CNS indications have moved forward in recent years, e.g. FDA approval for an ASO used for spinal muscular atrophy and several clinical trials for other neurodegenerative diseases such as Huntington's disease and ALS in progress. ASOs are attractive therapeutic candidates for diseases caused by known genetic abnormalities because they can manipulate target mRNA to modify or block protein production.

ASOs are unable to cross the blood-brain barrier, so they must be administered centrally. Despite the use of the intrathecal route in most studies testing ASOs for brain and spinal cord diseases, the CNS distribution of ASOs after intrathecal administration and the factors that help or hinder this distribution have not been well described in the literature. Here, we investigated ASO transport in the CNS, focusing on the effects of different ASO chemistries and the two mechanisms thought to govern the distribution of macromolecules in the brain: diffusion through extracellular spaces and convective flow through perivascular spaces (Pizzo et al. *J Physiol*, 2018).

We compared the diffusion and CNS distribution of two different clinically relevant ASO chemistries: a 1st generation phosphorothioate-modified ASO and a 2nd generation ASO with a 2' sugar modification. Both ASOs were covalently attached to AF488 fluorophores for detection. ASO free diffusion was measured in dilute agarose using integrative optical imaging, yielding free diffusion coefficients (37°C) of 1.88 ± 0.03 x 10^{-6} cm^2/s (mean ± sem; n=29) and 2.14 ± 0.02 x 10^{-6} cm^2/s (mean ± sem; n=14) for the 1st generation ASO and the 2nd generation ASO,

respectively, and apparent hydrodynamic diameters of approximately 3-4 nm for each monomer, as expected.
Intrathecal administration of the same ASOs was conducted in rats and the resulting distribution was visualized using *ex vivo* fluorescence and confocal microscopy. Our preliminary results showed a substantially more limited distribution for the 1st generation ASO as compared to the 2nd generation ASO. This comparison suggests that ASOs may experience additional sources of hindrance aside from size (e.g. binding or electrostatic interactions) that may limit their distribution in the brain.

Disclosures: M.E. Pizzo: None. **R.G. Thorne:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.24/TT1

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH grant R01 NS 38632

Title: Altered cerebral capillary densities and cognitive performance in neuronal HIF-1α/HIF-2α knockout mice

Authors: J. C. LAMANNA, V. MISTRY, A. ABDOLLAHIFAR, *K. XU
Dept Physiology/Biophysics, Case Western Reserve Univ., Cleveland, OH

Abstract: Hypoxia-inducible factor-1α (HIF-1α) and hypoxia-inducible factor-2α (HIF-2α) are transcription factors critical to the neurobiological response to hypoxia, a condition when the body is low in oxygen, by inducing short-term vasodilation and long-term angiogenesis. Angiogenesis is also strongly related to cognitive improvements. In this study we investigated the effect of neuronal knockout of HIF-1α/HIF-2α on cerebral capillary densities and cognitive performance and in mice. We use floxed HIF-1α/HIF-2α (HIF-1α$^{F/F}$ /HIF-2α$^{F/F}$) as controls. For neuronal knockout (KO), calcium/ calmodulin-dependent kinase (CAMKII)-Cre were used. Mice were 2-3 months of age. Y-maze tests were used to evaluate cognitive function. Microvascular density (N/mm^2) was determined by GLUT-1 immunohistochemistry. The capillary density in neuronal HIF-1 KO mice (451 ± 56, n = 6) was similar to that of the control mice (413 ± 57, n =8). Compared to the control mice, the neuronal HIF-2α KO mice had significantly higher capillary density in cortical brain (422 ± 64, n =8 vs. 498 ± 60, n = 7). The HIF-2α KO mice and HIF-1α/HIF-2α KO mice showed a decrease in cognitive Y-maze performance (presented as decreased alternation rate or decreased activity for exploring). Our data suggest that knockout of neuronal HIF-1α/HIF-2α altered the baseline brain capillary density and cognitive performance, HIF-1α and HIF-2α may play different roles in controlling capillary density in brain.

Disclosures: J.C. LaManna: None. **V. Mistry:** None. **A. Abdollahifar:** None. **K. Xu:** None.

Poster

677. Brain Blood Flow, Metabolism, and Homeostasis: Blood Brain Barrier

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 677.25/TT2

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: A constrained model of extracellular space using literature parameters and Monte Carlo simulation

Authors: *C. NICHOLSON
Physiol. & Neurosci., New York Univ., New York, NY

Abstract: I present a constrained 3D model of the ECS in rodent cortex using literature data derived from studies of molecular diffusion in the extracellular space (ECS) combined with Monte Carlo simulation. Measurements using the Real-Time Iontophoresis method with tetramethylammonium give a typical tortuosity value of 1.6 and a volume fraction of 0.2 [1]. This may be decomposed into a contribution of tortuosity = 1.2 for the interstitial viscosity [2], and a contribution of tortuosity = 1.33 from geometrical constraints. Packed convex cells separated by a uniform ECS width are known to only contribute tortuosity = 1.18 for this volume fraction [3] meaning that dead-space microdomains must make up the missing geometrical tortuosity. Measurements with the Integrated Optical Imaging method using macromolecules of different sizes together with application of restricted diffusion theory suggest that the typical width of the ECS is 40 nm [4] [5]. This set of constraints determines a basic cellular structure (BCS), which is arrived here at by Monte Carlo simulation. The ECS models consisted of 32 x 32 x 32 BCS each comprised cubes of side 2*a* with either cubic voids of side *b* ("sheets and voids model") or tunnels with square cross-section of side *b* ("sheets and tunnels model" [6]) to form the dead spaces. The BCS were separated by 40 nm. An instantaneous point-source of 25000 point molecules was placed in the ECS in the center of the BCS ensemble and a Monte Carlo simulations performed with MCell software [7] using a range of *a* and *b* values and the resulting tortuosities measured. It was found that there were unique values of *a* and *b* that resulted in tortuosity = 1.33.
References: [1] Sykova & Nicholson, Physiol. Rev. 88: 1277 (2008); [2] Zheng et al., Sci. Rep. 7: 422022 (2017); [3] Tao & Nicholson, J. Theoret. Biol. 229: 59 (2004); [4] Thorne & Nicholson, PNAS 103: 5567 (2006) [5] Nicholson & Hrabetova, Biophys. J. 113: 2133 (2017); [6] Kinney et al. J. Comp. Neurol. 521: 448 (2013); [7] www.mcell.org.

Disclosures: C. Nicholson: None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.01/TT3

Topic: F.08. Biological Rhythms and Sleep

Support: UNAM-DGAPA-PAPIIT IA207316
UNAM-DGAPA-PAPIIT IN224417

Title: Sleep in crayfish: Relation between brain electrical activity and autonomics variables

Authors: M. OSORIO-PALACIOS, I. OLIVER-DOMÍNGUEZ, L. MONTIEL-TREJO, *K. MENDOZA-ANGELES, J. HERNÁNDEZ-FALCÓN
Univ. Nacional Autónoma de México, México, Mexico

Abstract: In vertebrates like mammals and birds two types of sleep have been described: rapid eye movement (REM) sleep and no-REM sleep. Each one has a specific brain electrical activity, and is accompanied of changes in cardiac and respiratory frequencies. Slow wave sleep has been described in some invertebrates. Crayfish sleep fulfills behavioral and electrophysiological criteria defined for vertebrates. In this animal, heart and respiratory frequencies are modified by diverse changes in its environment during wakefulness. However, we do not know if this animal has sleep phases and what is the behavior of cardiorespiratory activity during sleep. The main goal of this work was to search for sleep phases in crayfish, and if there is any correlation with cardiorespiratory activity. We used adult male crayfish *Procambarus clarkii* in intermolt, synchronized to light-dark cycles 12:12. In cold anesthetized animals we implanted electrodes on deutocerebrum, both gill chambers, and cardiac sinus. After two days of recovery, we recorded, simultaneously, behavioral and electrical activity during 8 continuous hours. For behavioral records, we defined three conditions of the animal: wandering, immobile or lying on one side, and associated each one with the time of recording. To analyze brain electrical activity for each condition we used wavelet transform. We measured cardiac and respiratory rates during all recording conditions. We found that crayfish can sleep lying on one side or when it is motionless. The depth of sleep (measured as the power of electroencephalographic activity) change over time and is accompanied by oscillations in cardiorespiratory frequency. In conclusion, we propose that in crayfish there are phases of sleep.

Disclosures: M. Osorio-Palacios: None. **I. Oliver-Domínguez:** None. **L. Montiel-Trejo:** None. **J. Hernández-Falcón:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.02/TT4

Topic: F.08. Biological Rhythms and Sleep

Support: VA Biomedical Laboratory Research and Development Career Development Award #IK2 BX002712
Portland VA Research Foundation
Brain and Behavior Foundation NARSAD Award
Collins Medical Trust
NIH EXITO Institutional Core #UL1GM118964
NIH T32 5T32AA7468-29

Title: Validation of developmental sleep disruption using an orbital shaker in the prairie vole (microtus ochrogaster)

Authors: *M. E. KAISER, C. E. JONES[1], R. A. OPEL[2], M. M. LIM[3,4]
[1]Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR; [2]Portland VA Res. Fndn., Portland, OR; [3]Veterans Affairs Portland Hlth. Care Syst., Portland, OR; [4]OHSU, Portland, OR

Abstract: Early life sleep may play a critical role in development of adult behaviors. Research in our lab suggests that prairie voles (*Microtus ochrogaster*) subjected to early life sleep disruption (ELSD) have a reduced preference for a mate, increased neophobia, and locomotor hyperactivity as adults. Sleep disruption was accomplished by housing litters of voles on a standard laboratory orbital shaker for one week with both parents present in the home cage. In two experiments, we validated the specificity of this method for early life sleep disruption by 1) characterizing sleep stages in juvenile prairie voles housed both on and off the shaker, and 2) observing parental care during ELSD (to eliminate the possibility that the altered behavior observed in ELSD prairie voles later in life is caused by a change in parental care due to sleep disrupted parents). Nine young prairie voles underwent sleep EEG recordings for three days on the orbital shaker and three days at baseline, with order pseudo-randomized. EEG results showed that the orbital shaker caused fragmentation of NREM sleep and reduction of REM sleep. Next, 12 litters of voles (age 14-21 days) were recorded in the morning and afternoon and scored for parental care behaviors such as nursing, huddling, stereotypy, and lack of interaction with pups. Sleep disrupted parents did not significantly alter the total amount of care provided over the 7 day sleep disruption paradigm. In summary, our orbital shaker protocol significantly disrupts sleep in developing pups, while not significantly diminishing total parental care in either male or female parents, indicating that ELSD effects on behavior are likely specific to sleep disruption rather than disruption in parental care received.

Disclosures: C.E. Jones: None. **R.A. Opel:** None. **M.M. Lim:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.03/TT5

Topic: F.08. Biological Rhythms and Sleep

Support: VA Biomedical Laboratory Research & Development (BLR&D) Career Development Award (CDA) # IK2 BX002712
NIH T32 5T32AA7468-29
NIH EXITO Institutional Core, # UL1GM118964
Brain & Behavior Foundation NARSAD Award
Portland VA Research Foundation
Collins Medical Trust

Title: Dendritic spine density and morphology on prefrontal pyramidal neurons is altered in adult prairie voles after early life sleep disruption

Authors: *A. Q. CHAU[1], C. E. JONES[2], P. TEUTSCH[1], R. OLSON[1], M. M. LIM[1,2]
[1]Veterans Affairs Portland Hlth. Care Syst., Portland, OR; [2]Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Synaptic pruning during development allows for maintenance of proper connections and the elimination of aberrant ones. Rapid eye movement (REM) sleep is critical for pruning and maintaining new synapses formed during both development and learning. We hypothesize that disrupting REM sleep early in life will result in long lasting changes in synaptic density in cortical brain regions. The prefrontal cortex (PFC) is a late-maturing region that modulates higher order social and cognitive functions. Abnormally high dendritic spine density in the PFC is implicated in neurodevelopmental disorders. Emerging research in our lab suggests that selectively suppressing REM sleep early in life in the socially monogamous prairie vole (Microtus ochrogaster) impairs social development and increases inhibitory interneurons in the PFC. Using Golgi-Cox staining in adult prairie vole post-mortem tissue, we quantified dendritic spines in the prefrontal cortex in adult animals that underwent early life sleep disruption (ELSD). In males, ELSD increased spine density and decreased spine width selectively in the apical oblique distal (> 90 μm) segments of pyramidal neurons in prelimbic cortex layers II/III. Distal dendrites reflect long range inputs from further cortical and thalamic regions, suggesting that ELSD may lead to an impaired ability to integrate sensory information. Ongoing work will examine dendritic spine density and morphology earlier in development and in additional brain regions, including other brain regions and layers of the PFC. Results from these studies will

enhance our understanding of how modulation of sleep early in life contributes to the neuropathology of developmental disorders.

Disclosures: A.Q. Chau: None. **C.E. Jones:** None. **P. Teutsch:** None. **R. Olson:** None. **M.M. Lim:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.04/TT6

Topic: F.08. Biological Rhythms and Sleep

Support: VA Biomedical Laboratory Research & Development (BLR&D) Career Development Award (CDA) # IK2 BX002712
Portland VA Research Foundation
Brain & Behavior Foundation NARSAD Award
Collins Medical Trust
NIH EXITO Institutional Core #UL1GM118964
NIH T32 5T32AA7468-29
The Florida State University

Title: Early life sleep disruption increases cortical parvalbumin and impairs social and behavioral development in prairie voles

Authors: *M. M. LIM[1,2], A. Q. CHAU[1], D. L. COCKING[1], J. R. QUINTANA[3], E. A. HAMMOCK[3], C. E. JONES[2,1]
[1]Veterans Affairs Portland Hlth. Care Syst., Portland, OR; [2]Neurol., Oregon Hlth. & Sci. Univ., Portland, OR; [3]Psychology, Florida State Univ., Tallahassee, FL

Abstract: Across species, juveniles sleep more compared to adults, with disproportionately more time spent in REM sleep stages in the young. One function of REM sleep may be to facilitate the timing of GABAergic parvalbumin interneuron expression in the developing brain, a function critically important for tuning of excitation and inhibition. Here, we show that one week of REM sleep deprivation during a sensitive postnatal window of development increases parvalbumin-immunoreactivity in the cortex of prairie voles (*Microtus ochrogaster*), a highly social rodent species that forms lifelong pair bonds with other individuals. Prairie voles subjected to this protocol of early life sleep disruption failed to form pair bonds, showed locomotor hyperactivity, and showed more neophobia when presented with novel objects, compared to control subjects. There was a strong effect of sex on both parvalbumin-immunoreactivity and behavior testing, with impairments predominating in male animals. Taken together, these results may be reminiscent of the pathology and phenotype seen in autism spectrum disorder, a developmental

disorder characterized by disrupted sleep, altered cortical parvalbumin, and social impairment. We propose that sleep in early life plays a crucial role in the tuning of inhibitory neural circuits and the subsequent development of species-typical social behavior, and that sleep itself may play a causal role in the pathogenesis of neurodevelopmental disorders.

Disclosures: M.M. Lim: None. **A.Q. Chau:** None. **D.L. Cocking:** None. **J.R. Quintana:** None. **E.A. Hammock:** None. **C.E. Jones:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.05/TT7

Topic: F.08. Biological Rhythms and Sleep

Support: VA Biomedical Laboratory Research & Development (BLR&D) Career Development Award (CDA) # IK2 BX002712
Portland VA Research Foundation
Brain & Behavior Foundation NARSAD Award
Collins Medical Trust
NIH EXITO Institutional Core #UL1GM118964
NIH T32 5T32AA7468-29

Title: Acute footshock stress increases ethanol preference in adult prairie voles after early life sleep disruption

Authors: *C. E. JONES[1,3], P. TEUTSCH[3], A. E. RYABININ[1], M. M. LIM[2,3]
[1]Behavioral Neurosci., [2]Neurol., Oregon Hlth. & Sci. Univ., Portland, OR; [3]VA Portland Healthcare Syst., Portland, OR

Abstract: Early postnatal experience is important for shaping the development of the stress response. Across species, juveniles sleep more compared to adults, and early life sleep may represent an environmental factor associated with later life dysregulation of the behavioral and physiological response to stress. We show that one week of early life sleep disruption (ESLD) during a sensitive postnatal window of development interferes with the development of cortical GABA-ergic interneurons and impedes normal social development in the prairie vole (*Microtus ochrogaster*), a translational rodent model of social attachment. In addition to social impairments, adult prairie voles subjected to ELSD showed increased ethanol preference and ambulation in an open field after an acute footshock stressor, compared to control animals. This is reminiscent of neurodevelopmental disorders in humans that include comorbid anxiety and enhanced stress reactivity. We propose that early life sleep has a crucial role in the development

of neural circuits that underlie species-typical social behavior and stress reactivity, and that disrupted sleep may play a causal role in the pathogenesis of neurodevelopmental disorders.

Disclosures: C.E. Jones: None. **P. Teutsch:** None. **A.E. Ryabinin:** None. **M.M. Lim:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.06/TT8

Topic: F.08. Biological Rhythms and Sleep

Support: NIH R21 NS085757
NIH R01 NS103529

Title: Taar1 agonism promotes wakefulness without impairment of cognition in cynomolgus macaques

Authors: *A. V. GOONAWARDENA[1], S. R. MORAIRTY[1], R. DELL[1], T. WALLACE[1], A. WILLOUGHBY[1], M. C. HOENER[2], T. S. KILDUFF[1]
[1]Ctr. for Neurosci., SRI Intl., Menlo Park, CA; [2]F. Hoffmann-La Roche, Basel, Switzerland

Abstract: Trace amine-associated receptor 1 (TAAR1) is a GPCR with affinity for the trace amines. TAAR1 agonists have pro-cognitive, antidepressant- and antipsychotic-like properties in both rodent and non-human primates (NHPs). TAAR1 agonism has also been shown to increase wakefulness and suppress REM sleep in both mice and rats and to reduce cataplexy in two mouse models of narcolepsy. We investigated the effects of TAAR1 agonism in Cynomolgus macaques, a diurnal species that exhibits consolidated night-time sleep. We also extended our evaluation of the cognitive-enhancing potential of TAAR1 agonists in macaques by testing the acute effects of a TAAR1 partial agonist in a delayed match-to-sample (DMTS) test of working memory (WM). Adult, male Cynos (n=6) were implanted with epidural electroencephalograph (EEG) electrodes above left and right frontal cortex referenced to occipital cortex (Fp1-Oz and Fp2-Oz), and electromyogram (EMG) electrodes in the trapezius. Animals were kept under LD12:12; all studies were within-subject designs. For the sleep study, the partial TAAR1 agonist RO5263397 (0.1, 1 and 10 mg/kg; p.o.) was administered 30 min prior to lights off. EEG/EMG activity was scored in 30s epochs using guidelines of the American Academy of Sleep Medicine for scoring human sleep records and polysomnographic and spectral power measures were assessed during the initial 6h [Zeitgeber hour (ZT)13 to 18] following lights off. For cognition, animals were trained on a visual DMTS test to assess WM using 2 and 10-sec delays between the sample and choice phases; correct choices were rewarded with a food pellet. The same doses of RO5263397 were administered 30 min prior to testing DMTS. When compared to vehicle (VEH) treatment, R05263397 (10mg/kg) produced significant increases in Wake from ZT15 to ZT18,

reductions in both REM (ZT16 and ZT18) and NREM (ZT16 to ZT17) sleep, increases in wake after sleep onset (WASO) and decreases in sleep efficiency, NREM/REM cycles and REM/NREM ratio. EEG power analysis revealed significant increases in delta and theta power and reductions in alpha, sigma and beta power during Wake and significant increases in delta power and decreases in alpha, sigma, beta and low gamma power during REM sleep following the 10mg/kg dose compared to VEH. No significant change in DMTS accuracy (% correct) was observed at either delay at any dose of R05263397 compared to VEH, a paradigm previously shown to produce deficits with diazepam. These results indicate that effects of the TAAR1 partial agonist R05263397 has wake-promoting and REM-inhibiting effects on NHP sleep as previously described in rodents, properties that are desirable in a narcolepsy therapeutic.

Disclosures: A.V. Goonawardena: None. **S.R. Morairty:** None. **R. Dell:** None. **T. Wallace:** None. **A. Willoughby:** None. **M.C. Hoener:** None. **T.S. Kilduff:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.07/TT9

Topic: F.08. Biological Rhythms and Sleep

Support: CONACYT 243333 to CC
CONACYT 243247 to JRE
VIEP-BUAP 2018 and CA in Neuroendocrinología BUAP-CA-288.

Title: Sleep rebound after acute stress exposure in high- and low- yawning sublines of rats

Authors: *A. FIERRO-ROJAS[1], C. CORTES[1], J. EGUIBAR[1,2]
[1]Lab. of Behavioral Neurophysiol. and Motor Control. Inst. of Physiol, [2]Res. Office, VIEP. Benemérita Univ. Autónoma de Puebla., Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: The sleep rebound is a homeostatic response that varies in base of the susceptibility of the subjects (Ss). Stress exposure during wake time can lead to a change on sleep-wake pattern. Specifically acute stress exposure produces sleep rebound, which consists on an increase on sleep duration and sleep bouts due to a decrease in sleep-induced by stress. The sleep rebound can be observed during waking phase, 9 h after acute stress exposure and can last more than 6 h. We selectively bred two sublines from Sprague-Dawley rats which differ on their spontaneous yawning frequency, high-yawning (HY) rats has a mean of 20 yawns/h and the low-yawning (LY) just 2 yawns/h. The LY rat also showed anxious responses when are evaluated on standardized tests compared to the HY. The aim of this study was to assess the changes in the sleep-wake pattern after acute stress on both sublines.

We used 8 male of HY and LY sublines at 3 months of age. All Ss were implanted to record EEG, EMG and EOG to characterized sleep-wake phases. Baseline EEG of 24 h were obtained on the first day beginning at 0800. The following day placed on acrylic restrictor for 60 min at 0700. During restrain we recorded every 5 min the behavior display including strong mobility, struggling, rotation, biting and audible vocalizations, and also light mobility such as: chewing, yawning, grooming, gnawing and number of fecal boluses. Then, an additional 24 h sleep-wake recording was made. All procedures followed the NIH rules and the protocol was approved by BUAP-IACUC.
Acute restraint induced strong mobility displayed in the first 5 min that decreased over time ($P<0.5$) in both sublines. Light mobility was higher after 45 min in the HY rat compared to the LY rat ($P<0.5$). After the acute restraint there was an increase of the number and duration of non-rapid eye movement sleep (NREM) in the HY 6 h after restraint stress ($P<0.5$), and there was also an increase on the number of rapid eye movements sleep (REM) bouts 9 h after restraint. However, LY rat during restrain displayed more strong behaviors and higher REM sleep rebound respect to HY ($P<0.5$).
In conclusion, LY rats are higher responders to acute stress that affect the homeostatic mechanisms of sleep supporting its anxious trait.

Disclosures: C. Cortes: None. **J. Eguibar:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.10/TT12

Topic: F.08. Biological Rhythms and Sleep

Support: HHMI

Title: GABAergic neurons in substantia nigra promote sleep

Authors: *D. LIU[1,2], C. MA[1,2], W.-C. CHANG[1,2], Y. DAN[1,2]
[1]Mol. and Cell Biol., Univ. of California Berkeley, Berkeley, CA; [2]Howard Hughes Med. Inst., Berkeley, CA

Abstract: Falling asleep is normally associated with the inhibition of arousal systems and decrease in voluntary motor activity. Lesion of the substantia nigra, an important nucleus for motor regulation, can cause hyperactivity and insomnia, suggesting that it could also play a role in sleep regulation. Here we show that GABAergic (γ-aminobutyric-acid-releasing) neurons in the substantia nigra pars reticulata (SNr) are causally involved in sleep regulation. Activation of these neurons, either optogenetically or chemogenetically, promoted both non-REM and REM sleep, while inactivation greatly increased wakefulness. Further examination of mouse behavior

showed that optogenetic activation of SNr GABAergic neurons modulated the naturally occurred behavior state transition. Anterograde and retrograde tracing showed that in addition to direct innervation of medial thalamus (mTH), superior colliculus and brainstem motor centers, SNr GABAergic neurons also project to wake-promoting neurons in arousal centers, allowing them to coordinate the modulation of motor activity and brain states. Activating the SNr projection to mTH significantly increased NREM sleep, possibly through its direct inhibition of thalamo-frontal activities. Finally, enhancing the excitatory inputs to SNr GABAergic neurons by activating the neurotensinergic neurons in subthalamic nucleus (STN) also promoted NREM sleep. Together, these results revealed the involvement of a motor suppression circuit - STN-SNr-mTH - in sleep regulation.

Disclosures: D. Liu: None. **C. Ma:** None. **W. Chang:** None. **Y. Dan:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.11/TT13

Topic: F.08. Biological Rhythms and Sleep

Support: MH059839
MH115470

Title: Contextual fear conditioning produces robust sex differences in non-freezing behaviors and hippocampal EEG activity

Authors: *P. A. GEIST, S. DATTA
Univ. of Tennesee, Knoxville, TN

Abstract: Pavlovian fear conditioning has been routinely used as an animal model of human stress and anxiety disorders. However, fear conditioning studies have produced results with limited translational value to human research. In this study, we used holistic behavior categorization, hippocampal EEG recordings, and defecation as a sign of sympathetic activation to more closely approximate human fear. To accomplish this, ten male and ten female Sprague-Dawley rats with chronically implanted hippocampal EEG recording electrodes underwent a four-day contextual fear-conditioning paradigm. After each experimental condition, EEG activity was continuously recorded for twenty-one hours of their sleep-wake activities. Contextual fear-conditioning (CFC) behaviors were categorized as exploration, grooming, fleeing, apprehension, or freezing. We used Fast Fourier Transforms (FFT) to analyze EEG activity. The results of this study revealed a sex-dependent change in time spent in each behavior. Males spent more time performing apprehensive behaviors while females predominantly froze. Females also showed a significant increase in defecation over males. Males and females also displayed different patterns

of fear-related behaviors that would have been overlooked if only freezing responses were measured. These results suggest differences between sexes in contextual fear training and fear extinction (CFE) processes. In addition, hippocampal EEG activity showed sex dependent effects. Males showed a decrease in delta power while females displayed an increase. Both males and females displayed an increase in theta power, but males displayed a significantly greater increase and displayed changes earlier than females. Examining the relationship between the EEG activity and fear behaviors, hippocampal EEG activity and time spent in fear behavior were significantly correlated only when apprehensive behaviors were included with freezing behavior. These results demonstrate that combining more robust non-freezing behavioral and physiological fear responses can improve fear conditioning studies. Due to the highly conserved nature of physiological fear responses across species, this has important implications for the improved translation of animal research to human therapies.

Disclosures: P.A. Geist: None. **S. Datta:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.12/TT14

Topic: F.08. Biological Rhythms and Sleep

Support: MH059839
MH115470

Title: Brain derived neurotrophic factor mediates regulation of sleep and cognition via changes in synaptic transmission

Authors: *R. D. THAKKAR[1], P. A. GEIST[4], J. GARNER[2], S. DATTA[3]
[1]Dept. of Psychology, [3]Anesthesiol. and Psychology, [2]Univ. of Tennessee, Knoxville, TN; [4]Univ. of Tennesee, Knoxville, TN

Abstract: Brain derived neurotrophic factor (BDNF) is a widely expressed neurotrophic factor in the brain. Its role in growth, differentiation, and maintenance of neurons is well known. We have recently shown that heterozygous BDNF global knockdown (KD) leads to memory deficits and alterations in cortical and hippocampal EEG power in male and female rats. We further confirmed that this KD also led to significant reduction in REM sleep in both male and female rats. However, the molecular mechanisms underlying these cognitive and sleep changes remain to be understood. In the present study, we used protein analyses to examine the expression of molecular markers that regulate synaptic transmission in the cortex and hippocampus of wild-type and BDNF KD rats. The results of this study revealed that the expression of post-synaptic density marker, PSD95, was significantly reduced in male and female BDNF KD rats. However,

the expression of pre-synaptic markers like, synaptophysin and vesicular glutamate transporter 2 (vglut2), was increased in the BDNF KD male and female rats. These results suggest that BDNF-mediated regulation of these markers is lost, leading to disruption in synaptic transmission, following BDNF KD. These changes in synaptic markers, in both male and female rats, are correlated to BDNF-mediated changes in sleep and cognition. Collectively, our studies show that BDNF may drive cognitive plasticity, coordinate EEG activity, and modulate REM sleep via regulation of synaptic markers. Our study contributes to the understanding of altered BDNF pathways and the impact of downstream molecular signaling on sleep and cognition. This novel understanding may be useful for the development of therapeutic targets for neurodegenerative disorders as well as several psychiatric disorders that present sleep and cognitive deficits.

Disclosures: R.D. Thakkar: None. **P.A. Geist:** None. **J. Garner:** None. **S. Datta:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.13/TT15

Topic: F.08. Biological Rhythms and Sleep

Support: MH059839
MH115470

Title: A novel insight into the relationship between depression and sleep: The transitional sleep period between non-REM and REM sleep is altered in a depressive rodent phenotype

Authors: *A. BARNES[1], S. DATTA[2]
[1]Anesthesia Res., Univ. of Tennessee Hlth. Sci. Ctr., Knoxville, TN; [2]Anesthesiol. and Psychology, Univ. of Tennessee, Knoxville, TN

Abstract: Sleep alterations are well-documented phenomena in depressive disorders. The two most common observations are altered sleep spindles and reduced REM (Rapid Eye Movement) sleep latency. Interestingly, sleep spindles are observed in Stage 2 non-REM sleep and in the transitional sleep stage (tR) between non-REM and REM sleep. However, the biological mechanisms involved in tR are not well understood, and depression-related changes in tR have not been investigated. These unexplored changes in tR could reveal a relationship between depression-related alterations in non-REM and REM sleep, as well as provide insight into the biological mechanisms of tR. Here, we hypothesize that a long photoperiod model of depression in rodents produces changes in tR, and these changes are associated with changes in non-REM sleep architecture. Twelve control (n=6 male, n=6 female) and twelve experimental (n=6 male, n=6 female) rats were implanted with electrodes to enable the recording of sleep-wake (S-W) activity. Then, control animals were housed in a normal (12L:12D) light cycle, and experimental

animals were housed in a long photoperiod (21L:3D) light cycle. S-W activity was recorded for 24 hrs every four days for two weeks, and recordings were scored for wakefulness, non-REM, REM, and tR sleep. After two weeks, animals were tested for anxious, anhedonic and helpless behaviors. The results of this study revealed that long photoperiod rats showed increases in tR compared to control rats, and the largest increases occurred within the first hours of the altered light cycle. This increase in tR was not related to an increase in REM sleep. However, in long photoperiod animals, a reduction in REM sleep latency from Day 1 to Day 13 was observed. Additionally, the relationship between non-REM and REM sleep architecture was visibly altered in the long photoperiod condition compared to controls. No sex differences were observed. The results of this study suggest that changes in tR could be involved in the neurobiological underpinnings of depression-related sleep changes. Additionally, these results imply that there may be overlap between the biological basis of depression and the neural mechanisms involved in transitioning from non-REM to REM sleep.

Disclosures: A. Barnes: None. **S. Datta:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.14/TT16

Topic: F.08. Biological Rhythms and Sleep

Support: MH059839
MH115470

Title: Sleep deprivation increases the duration of ketamine anesthesia and selectively potentiates latency of post-anesthesia rapid eye movement sleep

Authors: *B. MITCHELL[1], P. A. GEIST[3], S. DATTA[2]
[1]Psychology, [2]Anesthesiol. and Psychology, Univ. of Tennessee, Knoxville, TN; [3]Univ. of Tennesee, Knoxville, TN

Abstract: Neuronal mechanisms which have evolved to generate traits of sleep are postulated to be involved in mediating the loss of consciousness produced by general anesthesia. Prior studies suggest that propofol anesthesia facilitates recovery from rapid eye movement (REM) and non-REM (NREM) sleep deprivation, but the relationship between dissociative anesthesia and sleep remains incompletely explored. In this study, we examined the effects of ketamine anesthesia on the sleep-wake (S-W) cycle and the extent to which this relationship is modulated by sleep deprivation. To achieve this, electrodes were chronically implanted in adult Sprague-Dawley rats to enable recording of S-W activity using cortical electroencephalogram (EEG), hippocampal EEG, and nuchal electromyography (EMG). After surgical recovery and habituation to recording

sessions, we administered an anesthetic dose of ketamine (100mg/kg, IP) to both non-sleep deprived and sleep deprived rats. Inspection of S-W activity revealed that ketamine anesthesia and subsequent dissociative symptoms suppressed the sleep (both NREM and REM) of all rats for about 6-7 hours. Upon recovery, both non-sleep deprived and sleep deprived rats exhibited a significant rebound in sleep during the dark phase. Analysis of sleep latency across condition revealed that sleep deprivation before ketamine selectively decreased the onset of the first REM sleep episode but did not affect the latency of NREM sleep. We also tested whether sleep deprivation potentiates the onset and duration of ketamine anesthesia—an effect reported in other intravenous and volatile anesthetics—and found that sleep deprivation did not speed up the onset of ketamine anesthesia but significantly extended its duration, suggesting that different categories of anesthetics have distinct interfaces with sleep profile. Taken together, these findings help to clarify the bidirectional relationship between sleep and dissociative anesthesia, and offer insight into shared neuronal mechanisms that generate traits of both states. Most importantly, our study helps determine whether ketamine is relevant for the clinical care of patients with sleep disorders by understanding its effects on sleep architecture in the perioperative setting.

Disclosures: B. Mitchell: None. **P.A. Geist:** None. **S. Datta:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.15/TT17

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CAPES Scholarship

Title: Differential effects of sex, estrous cycle and estradiol on the manic-like behaviors of locomotion, rearing and 50-kHz ultrasonic vocalizations induced by sleep deprivation in Wistar rats

Authors: *C. P. DE SOUZA[1], A. S. DORNELLAS[1], M. WÖHR[2], R. K. SCHWARTING[3], R. ANDREATINI[1]
[1]UFPR, Curitiba, Brazil; [2]Philipps-University of Marburg, Marburg, Germany; [3]Exptl. and Biol. Psychology, Philipps-University of Marburg, Marburg-Biedenkopf, Germany

Abstract: The manic state in Bipolar Disorder (BD) is composed of several complex signs including hyperactivity, pressured speech, hypersexuality, low need for sleep, and impulsivity. Although prevalence does not differ between sexes, symptomatology and comorbidities seem to differ in the clinic. There also seems to be an important influence of hormonal fluctuation and the reproductive cycle on the frequency and severity of manic episodes. Despite this, preclinical

studies with females and the evaluation of hormone fluctuation in mania animal models are scarce in the literature. Therefore, the objective of this study was to investigate the role of sex, estrous cycle and acute estradiol administration in manic-like behavior induced by 24h sleep deprivation (SD) in Wistar rats. Hyperlocomotion and rearing in the open field and the emission of 50-kHz ultrasonic vocalizations (50-kHz USVs), which are related to a state of positive affect, were evaluated. It was observed that female and male rats express different profiles of manic-like behaviors induced by SD. While female animals present higher hyperlocomotion and rearing, males present higher emission of 50-kHz USVs. In addition, it was observed that the estrous phase influences the emission of 50-kHz USVs, which led to an increased number of USVs in females in the peak hormonal phase (proestrus), compared to other estrous phases. This effect was not observed on rearing or locomotor activity. Lastly, it was observed that acute estradiol administration induces an increase in 50-kHz USVs, rearing and locomotor activity in ovariectomized female rats. Thus, we observed sexual differences in manic-like behavior induced by SD, as well as the influence of hormonal fluctuation, specifically the effect of estradiol. The analysis of 50-kHz USVs appears to be more sensitive to hormonal fluctuation in females than hyperlocomotion and rearing and therefore 50-kHz USV appears to be an important and sensitive behavioral parameter to assess the affective state in the mania models. These results support the idea that sex and sex hormones are important factors that need to be taken into consideration in animal modelling of psychiatric disorders.

Disclosures: C.P. De Souza: None. **A.S. Dornellas:** None. **M. Wöhr:** None. **R.K. Schwarting:** None. **R. Andreatini:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.16/TT18

Topic: F.08. Biological Rhythms and Sleep

Support: MH059839
MH115470

Title: Effects of an anesthetic dose of ketamine and sleep deprivation-induced rebound sleep on behavioral outcomes

Authors: *K. BURFORD[1], B. MITCHELL[2], R. D. THAKKAR[3], S. DATTA[4]
[1]Univ. of Tennessee-Knoxville, Knoxville, TN; [2]Psychology, Univ. of Tennessee, Maryville, TN; [3]Dept. of Psychology, [4]Anesthesiol. and Psychology, Univ. of Tennessee, Knoxville, TN

Abstract: Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to produce long-lasting behavioral effects at sub-anesthetic doses. However, the

relationship between an anesthetic dose of ketamine and exploration behavior has not been fully investigated. Parallel studies from our lab have indicated that an anesthetic dose of ketamine accrues sleep debt, resulting in a substantial rebound of sleep during the subsequent dark period. In the present study, we examined the effects of an anesthetic dose of ketamine combined with sleep-deprivation induced rebound sleep on exploratory behavior within an open-field paradigm. To achieve this, Sprague-Dawley rats were recorded for baseline cortical EEG and baseline exploratory behavior in the open-field box. Animals with normal sleep or rebound sleep were then subjected to an open-field trial before and after ketamine administration (100mg/kg, IP). The results of this study revealed that rebound sleep prior to testing led to more exploratory behavior in the open-field as compared to animals with a normal sleep profile. Interestingly, animals that received ketamine alone also displayed more exploratory behavior than those who did not receive ketamine, and combination of sleep deprivation and ketamine further potentiated this effect. However, there were no changes in the total locomotion, quantified as total distance traveled, in all three conditions. Taken together, these results suggest that sleep profile modulates the degree to which an anesthetic dose of ketamine increases exploratory behavior. These data suggest that an anesthetic dose of ketamine reduces basal anxiety, which may have implications for behavioral research in rodent models. Finally, our study provides greater insight into the effects of clinically relevant doses of ketamine on cognition and emotion.

Disclosures: K. Burford: None. **B. Mitchell:** None. **R.D. Thakkar:** None. **S. Datta:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.17/TT19

Topic: F.08. Biological Rhythms and Sleep

Support: SFB/f44
MSA Coalition
FWF Grant

Title: Reduced compensatory mechanisms following homeostatic sleep preasure in an animal model for MSA reflect impaired sleep quality in patients

Authors: *T. FENZL[1], L. HÄRTNER[2], V. LEIS[3], M. KREUZER[1], G. WENNING[2], N. STEFANOVA[2]
[1]Tech. Univ. Munich, Clin. For Anesthesio, Munich, Germany; [2]Med. Univ. Innsbruck, Innsbruck, Austria; [3]Leopold Franzens Univ., Innsbruck, Austria

Abstract: Objective and Rationale: Multiple system atrophy (MSA) is a rapidly progressive, fatal neurodegenerative disease. Clinical symptoms include parkinsonism, cerebellar ataxia and

autonomic failure. Sleep related symptoms, such as rapid eye movement sleep behavior disorder (RBD), breathing disorders and restless legs syndrome are also very common in MSA patients and precede MSA diagnosis. The PLP-αSYN mouse model for MSA (MSAm) is very well established with a strikingly similar behavioral phenotype, when compared to the clinical situation. Our recent findings of MSA-related sleep symptoms in MSAm strongly increased face validity and set the stage for a potential predictive validity for the first time. In the present study we challenged the homeostatic equilibrium between sleep and wakefulness to access and to evaluate general sleep quality in MSAm. Methods and Results: We performed chronic EEG recordings on six consecutive days in freely behaving, 24-week old, adult MSAm (n=6) and age-matched C57Bl6 (WT, n=6) control mice. At day 4 of the recording session each animal underwent a sleep deprivation (SD) for 6 hours, starting at experimental time 0 (lights on at 10am, light cycle 12h/12h). We induced sleep deprivation by gentle handling. Two experienced scorers that were blind to each other analyzed the EEG recordings with a semi-automatic scoring routine and a manual rescoring. We performed the temporal and spectral analyses based on these scores. Both, WT and MSAm showed a sleep rebound immediately after the 6h SD. MSAm had a stronger non rapid eye movement sleep (NREMS) rebound, whereas WT showed a stronger (and delayed) rapid eye movement sleep (REMS) rebound. SWA power was higher in the WT during the 2h after SD. In the first lights-off phase after SD, WT and MSAm showed a second NREMS rebound. This rebound happened later in the WT group. The WT animals also expressed higher SWA power during the active period (lights off). Further, WT also developed a second REMS rebound that we did not observe in the MSAm. Conclusions: The response of WT to SD resembles established findings from the relevant literature. In contrast, the circadian shift of compensatory mechanisms during NREMS and lack of rebound effects during REMS on a homeostatic challenge in MSAm clearly demonstrate impaired compensation mechanisms. Together with other EEG-based results in MSAm, previously established in our sleep research group, these profound findings may serve as potential biomarkers for early MSA diagnosis. Given that the development of MSA is combined with a progressive loss in neuronal and synaptic function, our findings in SWA after SD may also support the theory of synaptic homeostasis.

Disclosures: T. Fenzl: None. **L. Härtner:** None. **V. Leis:** None. **M. Kreuzer:** None. **G. Wenning:** None. **N. Stefanova:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.18/TT20

Topic: F.08. Biological Rhythms and Sleep

Support: Mission funds of the US Army Research Laboratory

Title: Inter-session reproducibility of brain network structure in resting and task states

Authors: *J. NAKUCI[1], J. O. GARCIA[3,4], N. WASYLYSHYN2W[3,4], S. H. THOMPSON[3,4], J. C. ELLIOTT[5], M. CIESLAK[6], B. GIESBRECHT[7], S. T. GRAFTON[7], J. M. VETTEL[8,4,6], S. F. MULDOON[2]
[1]Dept. of Mathematics, [2]Dept. of Mathematics and CDSE Program, Univ. at Buffalo, Buffalo, NY; [3]U.S. Army Res. Lab., Aberdeen Proving Ground, MD; [4]Dept. of Bioengineering, Univ. of Pennsylvania, Philadelphia, PA; [5]Dept. of Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA; [6]Dept. of Psychological and Brain Sci., [7]Univ. of California, Santa Barbara, CA; [8]Translational Neurosci. Br., Army Res. Lab., Aberdeen, MD

Abstract: Network analysis has provided new and important insights into the function of complex systems such as the brain by examining the topology of both structural and functional networks constructed from diffusion MRI, functional MRI (fMRI) and electro/magnetoencephalography (E/MEG) data. However, these studies are often limited to the analysis of a single recording or scanning session for each subject, or only compared between two subsequent sessions, raising questions about inter-session reproducibility. Given the prevalence of inter-subject variability in network statistics calculated across multiple subjects for data from a single session, it is important to characterize the reproducibility of network statistics across sessions to assess the sensitivity and stability of network measures to between subject variation. Here, we investigate the reproducibility of network statistics measured in human brain networks by comparing inter-subject and inter-session variability across multiple measures of network structure. We study structural and functional brain networks derived from diffusion imaging, fMRI, and EEG from 30 subjects with 8 sessions of rest and task recordings. The diffusion imaging networks were constructed using a probabilistic tracking algorithm. The functional fMRI networks were constructed using Wavelet-Coherence across five frequency bins from 0.06-0.1Hz. For EEG data, networks were constructed using the de-biased weighted Phase Lag Index (dwPLI) across five frequency bands: δ (1-3Hz), θ (3-7Hz), α (8-13Hz), β (15-30Hz), and γ (30-50Hz). For the resulting networks, we calculated the degree, clustering coefficient, path length, small-world topology, synchronizability, local and global efficiency, spectral radius, and eigenvalue centrality. The Interclass Correlation Coefficient (ICC) was used to assess inter- and intra-subject variability across each network measure. We find that intra-subject reproducibility is higher than inter-subject reproducibility, indicative of the ability to detect individual differences in network structure in human brain networks. Interestingly, for fMRI networks, intra-subject reproducibility increases with the level of cognitive demand associated with tasks. Furthermore, EEG, unlike fMRI, exhibits a dependence upon the frequency band studied, with α (8-13Hz) having consistently higher reproducibility across rest and task.

Disclosures: J. Nakuci: None. **J.O. Garcia:** None. **N. Wasylyshyn2W:** None. **S.H. Thompson:** None. **J.C. Elliott:** None. **M. Cieslak:** None. **B. Giesbrecht:** None. **S.T. Grafton:** None. **J.M. Vettel:** None. **S.F. Muldoon:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.19/TT21

Topic: F.08. Biological Rhythms and Sleep

Support: US ARMY RESEARCH LABORATORY W911NF-18-2-0064

Title: Longitudinal examination of naturalistic sleep, global brain dynamics, and visual working memory performance in healthy adults

Authors: *N. LAUHARATANAHIRUN[1,2], J. O. GARCIA[1], S. M. THURMAN[1], N. WASYLYSHYN[1], S. H. TOMPSON[1], M. CIESLAK[3], G. OKAFOR[3], B. GIESBRECHT[3], S. T. GRAFTON[3], E. FLYNN-EVANS[4], E. B. FALK[2], J. M. VETTEL[1]
[1]U.S. Army Res. Lab., Aberdeen Proving Ground, MD; [2]Annenberg Sch. for Communication, Univ. of Pennsylvania, Philadelphia, PA; [3]Psychological and Brain Sci., UC Santa Barbara, Santa Barbara, CA; [4]NASA, Mountain View, CA

Abstract: Sleep is essential for maintaining optimal physiology, behavior, and health. Sleep deprivation studies of 24 or more hours reveal impairments to neurocognitive performance. However, this knowledge is derived from substantial sleep loss in laboratory settings where performance is examined directly following sleep loss. In the real world, moderate and consistent sleep loss across days, weeks, or even months can occur, but it is not well understood how longitudinal effects of inadequate sleep influence performance. One central challenge for studying naturalistic sleep is that there is no clear consensus on what sleep parameters are critical for capturing decrements in neurocognitive performance. To address this gap, we use a longitudinal design to study how individual differences in naturalistic sleep influences bi-weekly neurobehavioral performance on a visual working memory (VWM) task.
For 16 consecutive weeks, participants (N=30) wore an Readiband Actigraph SBV2 wristwatch and completed daily sleep diaries to capture both objective and subjective metrics of sleep history. Daily sleep metrics were computed, including sleep duration, sleep efficiency, number of awakenings, and subjective reports of sleep quality. Participants came to the laboratory bi-weekly and completed a VWM task while BOLD responses were monitored using fMRI. Participants were asked to compare the location and color of a single square stimulus (easy) or six simultaneously presented stimuli (difficult) to a previously presented set of stimuli. BOLD data were averaged within 264 regions of a whole-brain atlas (Power et al., 2011), and functional connectivity was computed via wavelet coherence between all region pairs. A linear mixed-effects model was used to assess the relations among daily sleep metrics, pairwise functional connectivity between regions, and VWM performance across the 8 bi-weekly sessions.
Results indicated that sleep metrics derived from actigraphy explained the most variance in

VWM performance. Higher sleep efficiency (sleep duration divided by amount of time in bed) in the two-week period prior to each scan session was related to better VWM accuracy, while higher levels of intra-individual variability in sleep efficiency across the two-week period were related to lower VWM accuracy. Functional connectivity within task-active and aggregated across functional systems was also included as a moderator between sleep and VWM performance. In sum, these results provide evidence that naturalistic sleep fluctuations, especially sleep efficiency, produce systematic effects on cognition that are influenced by global brain dynamics.

Disclosures: N. Lauharatanahirun: None. **J.O. Garcia:** None. **S.M. Thurman:** None. **N. Wasylyshyn:** None. **S.H. Tompson:** None. **M. Cieslak:** None. **G. Okafor:** None. **B. Giesbrecht:** None. **S.T. Grafton:** None. **E. Flynn-Evans:** None. **E.B. Falk:** None. **J.M. Vettel:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.20/TT22

Topic: F.08. Biological Rhythms and Sleep

Title: Individual differences in state-based performance effects derived from functional connectivity in a 16 week longitudinal study

Authors: *K. R. GAMBLE[1], J. O. GARCIA[3], H. ROY[4], N. LAUHARATANAHIRUN[1], S. M. THURMAN[6], N. WASYLYSHYN[7], S. H. TOMPSON[5], M. CIESLAK[8], B. GIESBRECHT[10], S. T. GRAFTON[9], E. FALK[11], J. M. VETTEL[2]
[1]Army Res. Lab., Aberdeen Proving Ground, MD; [2]Translational Neurosci. Br., Army Res. Lab., Aberdeen, MD; [4]Human Res. Engin. Directorate, [3]U.S. Army Res. Lab., Aberdeen Proving Ground, MD; [5]U.S. Army Res. Lab., Aberdeen, MD; [6]Human Res. and Engin. Directorate, US Army Res. Lab., Playa Vista, CA; [7]Human Res. and Engin. Directorate, US Army Res. Lab., Philadelphia, PA; [8]Psychological and Brain Sci., [9]Psychological & Brain Sci., UCSB, Santa Barbara, CA; [10]Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA; [11]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Individuals have different strengths, and these individual differences help explain a person's overall performance on a given task over time, but performance in any given session can vary. Even experts sometimes perform badly, and can be equal or worse than novices under some circumstances (Beilock et al., 2002). These fluctuations are thought to reflect variability in physiology where modulations in the efficiency of brain dynamics might underlie variable task performance (Raichle, 2010). This relationship is often described in terms of brain state effects on performance. Here, we examine whether recent methodological developments from network

neuroscience (Telesford et al., 2016) can detect changes in brain network connectivity that may determine state-based fluctuations on task performance. Importantly, we utilize a longitudinal study to examine the robustness and stability of the relationship between connectivity and performance within-subject and across five diverse cognitive tasks.
Over four months, participants (N=30) completed eight bi-weekly experimental sessions where simultaneous fMRI/EEG brain data was recorded while they completed five cognitive tasks, including working memory, sustained attention, dynamic attention, emotional valence, and mental arithmetic. The brain was parcellated into 68 regions of a whole-brain atlas (Desikan et al., 2006), and background functional connectivity was computed separately for each imaging modality. The BOLD connectivity was calculated via wavelet coherence (averaged .06-.10Hz) between all region pairs, while the EEG connectivity was computed between pairs of band-passed EEG sources (cLORETA) using a phase locking value (Lachaux et al., 1999). The connectivity timeseries were then used in a community detection algorithm (Garcia et al., 2018) to identify data-driven communities that captured the strength of the relationship between all pairs of regions across time. A graph metric method was used to determine three measures of these communities: 1) network flexibility, how often a node switches between communities, 2) node disjointedness, the probability of a node switching communities on its own, and, 3) module allegiance, the probability that two nodes are in the same functional community (Bassett et al., 2015). Preliminary results found a robustness to the metrics within-task and across individuals, but some shared resources between tasks that may indicate an adaption to retain robust cross-task function. These results display the robust coordination of neural units across tasks, but also the sensitivity (or neural *fragility*) of these network dynamics to fluctuations in brain state.

Disclosures: K.R. Gamble: None. **J.O. Garcia:** None. **H. Roy:** None. **N. Lauharatanahirun:** None. **S.M. Thurman:** None. **N. Wasylyshyn:** None. **S.H. Tompson:** None. **M. Cieslak:** None. **B. Giesbrecht:** None. **S.T. Grafton:** None. **E. Falk:** None. **J.M. Vettel:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.21/TT23

Topic: F.08. Biological Rhythms and Sleep

Support: MH059839
MH115470

Title: The relationship between sleep and autonomic health in college students

Authors: *M. D. OLIVER, D. R. BALDWIN, S. DATTA
Univ. of Tennessee, Knoxville, TN

Abstract: Restrictions in sleep are associated with increased stress-related neuroendocrine system activation, which may induce alterations in autonomic control. Investigations into both sympathetic and parasympathetic branches of the Autonomic Nervous System (ANS) have shown that autonomic imbalances are precursors to cardiovascular disease, cognitive impairment, and other health-related risks. However, the relationship between aspects of sleep and ANS functioning remains to be poorly understood. Therefore, the present study examined the relationship between aspects of sleep and indices of ANS functioning in 141 undergraduate students (52 males and 89 females; mean age = 20.716 years). Participants completed a demographic survey and the Pittsburgh Sleep Quality Index (PSQI). **Next, physiological variables** [i.e. Skin Conductance (SC) and Heart Rate Variability (HRV)] were measured simultaneously for 5-minutes in order to assess ANS functioning at rest. Results revealed that SC was positively associated with sleep quality ($r = 0.187$, $p = 0.027$), sleep latency ($r = 0.173$, $p = 0.040$), use of sleep medication ($r = 0.306$, $p < 0.001$), and global PSQI score ($r = 0.188$, $p = 0.026$). Indices of HRV and sleep components yielded a negative association between the standard deviation of the normal-normal interval (SDNN) and the amount of time that it takes to fall asleep each night ($r = -0.173$, $p = 0.041$). Finally, sleep efficiency was negatively correlated with low frequency HRV ($r = -0.262$, $p = 0.002$) indicating that more effective sleep is associated with less sympathetic nervous system (SNS) activity. Findings of this study suggest that both quality and quantity of sleep are associated with autonomic activity at rest and may be a protective factor against negative consequences of SNS over-activation. Additionally, students need to be educated regarding the pitfalls of reliance upon sleep medication. Moreover, although sleep medication may promote the process of going to sleep, it has a paradoxical effect in that it is not sufficient enough to alter the effects of autonomic imbalance due to increased arousal and/or stress. Finally, our results show that sleep is an effective tool for the assessment of autonomic balance and cardiovascular health in college students.

Disclosures: M.D. Oliver: None. **D.R. Baldwin:** None. **S. Datta:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.22/TT24

Topic: F.08. Biological Rhythms and Sleep

Support: This project was supported by the Pac-12 Conference Student-Athlete Health & Well-Being Grant Program, Grant Reference # 2-02_Pac-12-Colorado-McQueen-16-01.

Title: Travel in collegiate varsity student-athletes: Relationship to mood across seasons and the factors that influence this relationship

Authors: *E. VILLEGAS, JR[1], D. MCCARTNEY[3], M. HOLLIDAY[2], A. BOHR[2], M. MCQUEEN[2], T. D. HERNANDEZ[4]
[1]Psychology and Neurosci., [2]Univ. of Colorado Boulder, Boulder, CO; [3]Univ. of Colorado, Boulder, CO; [4]Psychology and Neurosci., Univ. of Colorado at Boulder, Boulder, CO

Abstract: Travel for collegiate varsity student athletes during competitive season is a necessity, and may also be a significant stressor. Gaining an understanding of the factors that contribute to the stressful nature of competitive travel is important, as it holds the potential to uncover targets of opportunity for interventions aimed at minimizing the adverse consequences of competitive travel. To this end, the present study utilized the Brief Assessment of Mood (BAM) to assess mood disturbance and energy indices throughout two competitive seasons (fall 2016 and 2017) of Division I NCAA women's volleyball student athletes at the University of Colorado Boulder. In addition to quantitative measures of mood (BAM), qualitative information was also utilized to provide additional detail associated with BAM scores. Differences within each season and between the two seasons relating to mood disturbance and energy levels were assessed, as were potential factors that contributed to the differences. The main findings from the study include a consistent increase in mood disturbance after travel and an overall decrease in mood disturbance from fall 2016 to fall 2017. Additional findings from the study will be discussed in the context of how to minimize the adverse impact of travel as much as possible in collegiate varsity student athletes.

Disclosures: E. Villegas: None. **D. McCartney:** None. **M. Holliday:** None. **A. Bohr:** None. **M. McQueen:** None. **T.D. Hernandez:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.23/UU1

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant RO1 MH103318
NIH Grant T32 MH019934

Title: Age and gender-related associations between objective sleep measures and inflammatory markers in bipolar affective disorder

Authors: *E. E. LEE[1], C. KAUFMAN[2], L. T. EYLER[3]
[2]Psychiatry, [1]UCSD, La Jolla, CA; [3]Dept Psychiatry, UC San Diego, La Jolla, CA

Abstract: Objective:
To characterize the relationship between objective sleep measures and inflammatory markers in

persons with bipolar disorder (BD)**.**

Rationale:

Disrupted sleep is a hallmark symptom of BD, contributing to worse quality of life and psychopathology. BD patients also have elevated inflammatory markers. Studies have described a strong link between sleep disturbances and increased inflammation, though this has not been examined systematically in BD.

Methods:

We examined 35 subjects with BD and 57 healthy comparison subjects (HCs) (age 26-65 years), with mean age 48 years and matched on gender and race. During a 2-week burst, subjects had blood drawn 3 times for assays of cytokine and chemokine levels. Sleep parameters (total sleep time, sleep latency, sleep efficiency, number and length of awakenings, overall sleep fragmentation) was assessed nightly using wrist-worn actigraphy.

Results:

The BD group had significantly worse sleep measures and higher levels of inflammatory markers compared to the HCs. There were significant group x sleep measure interactions for IL-8 and IP-10 levels. Within the BD group, CCL-11, MCP-1, and MIP-1b levels were correlated with worse sleep measures. Focusing on the sleep during the night prior to the blood draw for inflammatory markers for all subjects, time-lag analyses showed that prior evening's sleep latency was significantly associated with CCL-11 and MCP-1 only in the BD group. Also, the prior night's sleep latency was significantly associated with MCP-1 and MIP-1b among women with BD but not men with BD; while sleep latency was associated with CCL-11 in both genders. Age was correlated with MCP-1 and TNF-alpha in both diagnostic groups. When controlling for age, the prior night's sleep latency remained significantly associated with MCP-1 in the BD group.

Conclusions:

There is some evidence of a link between sleep and inflammation in BD, which varies with gender and age. It is likely that other factors, i.e., depressive mood, physical activity, and diet, contribute to both sleep and inflammation and warrant further assessment. Furthermore, the directionality of the relationship between sleep and inflammation is not clear. Longitudinal data collected in this ongoing study will allow us to address directionality in the future.

Disclosures: E.E. Lee: None. **C. Kaufman:** None. **L.T. Eyler:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.24/UU2

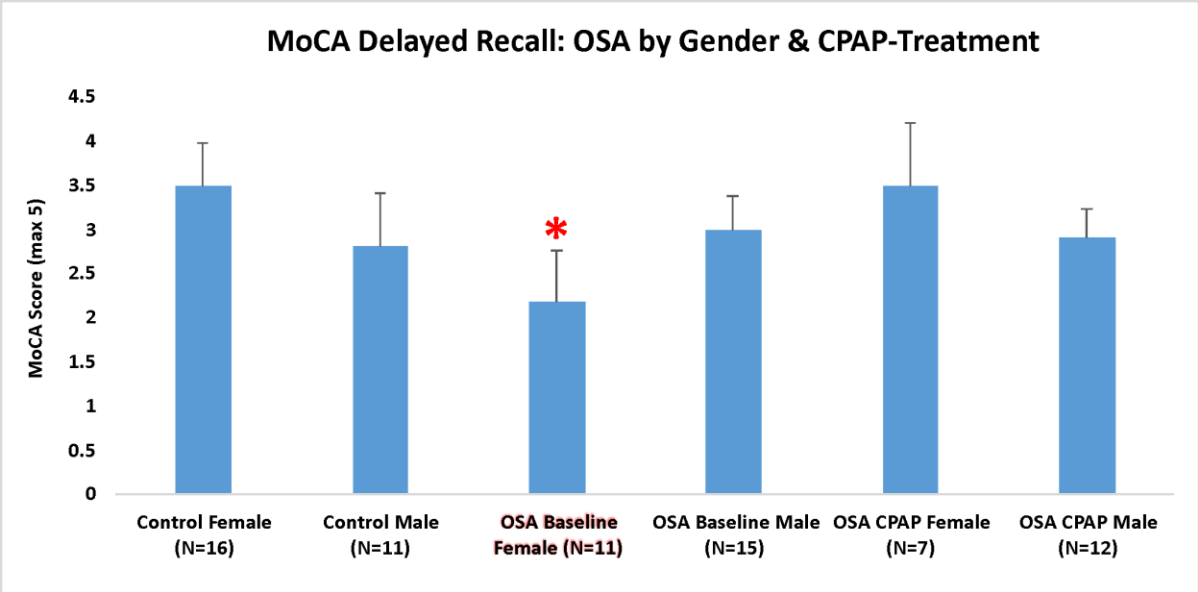
Topic: F.08. Biological Rhythms and Sleep

Support: NINR-013693

Title: Cognitive symptoms in females and males with obstructive sleep apnea

Authors: *D. M. ARON[1], A. P. AGUILA[1], H. L. SAFT[5], R. AYSOLA[2], J. A. OGREN[3], R. M. HARPER[4,3], P. M. MACEY[1,4]
[1]UCLA Sch. of Nursing, [2]Div. of Pulmonary and Critical Care, [3]Dept. of Neurobiology, David Geffen Sch. of Med. at UCLA, [4]Brain Res. Institute, David Geffen Sch. of Med. at UCLA, Univ. of California at Los Angeles, Los Angeles, CA; [5]Div. of Pulmonary and Critical Care, Natl. Jewish Hlth., Denver, CO

Abstract: Introduction: Impaired cognition is a common symptom of obstructive sleep apnea (OSA), possibly due to neural injury in such cognitive areas as the hippocampus. The extent of injury varies between females and males, and the degree and type of cognitive impairments are also likely to vary by sex.
Methods: We studied 72 subjects which included 26 untreated (15 male) and 19 CPAP-treated (12 male) OSA patients, and 27 healthy controls (11 male). Cognitive function was measured using the Montreal Cognitive Assessment (MoCA), a 10-minute test assessing 7 cognitive sub-domains, providing scores for each category, and an overall score out of 30 (<26 indicates cognitive impairment). We described the MoCA findings by group for overall and subdomain scores: visuospatial, naming, attention, language, abstraction, delayed recall, and orientation. Group differences were assessed by ANOVA ($P<0.05$ threshold).
Results: Two sub-domains that showed significant effects ($P<0.05$) were delayed recall (more impaired in untreated female OSA vs. all other groups) and attention (higher in untreated male OSA vs. all other groups). Male and female controls had the highest overall scores (25.8±3.8 [mean±std]), while the untreated male (25.2±2.7) and female (24.8±2.9) OSA groups scored the lowest, and the male and female CPAP groups scored 25.6±1.6 and 25.7±4.8 respectively. However, these group differences were not significant ($P>0.05$). Naming and visuospatial sub-domains showed trends towards significance.
Conclusions: The findings show that OSA, in this sample, was not associated with major cognitive impairment, but some alterations in attention occurred, as did deficits in memory, consistent with findings by others. These cognitive differences were sex-specific, supporting the hypothesis that neural injuries underlie the symptoms. The findings also suggest that, as shown previously, females with OSA suffer from specific cognitive symptoms, such as impaired verbal recall.



Disclosures: A.P. Aguila: None. **H.L. Saft:** None. **R. Aysola:** None. **J.A. Ogren:** None. **R.M. Harper:** None. **P.M. Macey:** None.

Poster

678. Sleep Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 678.25/UU3

Topic: F.08. Biological Rhythms and Sleep

Support: Mission funding from US Army Research Laboratory

Title: Linking naturalistic sleep fluctuations to the energy landscape in dynamic brain modules

Authors: *J. O. GARCIA[1,2], A. ASHOURVAN[2], S. M. THURMAN[1], N. WASYLYSHYN[1], S. H. TOMPSON[1], N. LAUHARATANAHIRUN[1,2], M. CIESLAK[3], J. C. ELLIOTT[3], G. OKAFOR[3], B. GIESBRECHT[3], S. T. GRAFTON[3], E. FLYNN-EVANS[4], D. S. BASSETT[2], J. M. VETTEL[1]
[1]U.S. Army Res. Lab., Aberdeen Proving Ground, MD; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]Univ. of California, Santa Barbara, Santa Barbara, CA; [4]NASA Ames Res. Ctr., Mountain View, CA

Abstract: Sleep plays a critical role in everyday biological functions, and the lack of adequate sleep has been widely linked to performance impairments in a variety of task domains (Van Dongen et al., 2004). To account for these impairments, the wake-state instability theory (Doran et al., 2001) posits that variability in performance reflects competition between two

neurobiological systems working to reciprocally inhibit the other: one system promoting sleep as homeostatic pressure accumulates, and the other fighting to maintain wakefulness (Killgore, 2010). Yet, this neurobiological process is still not well understood due to limitations of prevailing analytical techniques in measuring and tracking momentary changes in dynamic mental states.
To overcome this hurdle, we propose that state instability may be modelled by estimating the energy landscape of network transitions via a maximum entropy model (MEM) built upon dynamic network properties of the brain (Ashourvan et al., 2017). Borrowed from statistical mechanics, a MEM framework describes transitions between evolving states as a series of stays and transitions between different attractors in the system, successfully modelling ensemble neuronal activity (Tang et al., 2008), predicting perception (Watanabe et al., 2014a), and estimating sleep stage transitions (Watanabe et al., 2014b).
In a 16-week longitudinal study, participants (N=30) wore an actigraphy wristwatch and completed daily sleep diaries to capture objective and subjective measurements of their naturalistic sleep history (Thurman et al., 2018). During these 4 months, participants also completed a series of cognitive tasks and a resting state scan while brain activity was measured with biweekly fMRI/EEG recordings. We estimated the energy landscape (Ashourvan et al., 2017) in 4 steps: (1) calculated functional connectivity in discrete time bins in both the fMRI BOLD timeseries and band-passed EEG sources (cLORETA), (2) performed community detection of dynamic networks by optimizing a modularity quality function (Garcia et al., 2018), (3) fitted a pairwise MEM to the state of co-occurrence timeseries of each ROI, and (4) extracted features surrounding local energy minima. Our analysis found that increasing levels of sleep debt increased the energy requirements to change among the data-derived network communities from both the rest and task brain activity. Our findings suggest broad network dynamics in both the energy landscape estimated within BOLD-fMRI and oscillatory sources measured with EEG are associated with naturalistic fluctuations in sleep, suggesting a higher sensitivity of network dynamics to the impact of sleep.

Disclosures: J.O. Garcia: None. **A. Ashourvan:** None. **S.M. Thurman:** None. **N. Wasylyshyn:** None. **S.H. Tompson:** None. **N. Lauharatanahirun:** None. **M. Cieslak:** None. **J.C. Elliott:** None. **G. Okafor:** None. **B. Giesbrecht:** None. **S.T. Grafton:** None. **E. Flynn-Evans:** None. **D.S. Bassett:** None. **J.M. Vettel:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.01/UU4

Topic: F.08. Biological Rhythms and Sleep

Support: NIH 5R01NS094211-02

UW Institute for Neuroengineering and Washington Research Foundation Innovation Graduate Fellowship in Neuroengineering

Title: Circadian regulation of sleep in a mouse model of Dravet syndrome

Authors: *R. E. SANCHEZ[1], I. BUSSI[2], M. BEN-HAMO[2], H. O. DE LA IGLESIA[3]
[1]Grad. Program in Neurosci., The Univ. of Washington, Seattle, WA; [3]Biol., [2]Univ. of Washington, Seattle, WA

Abstract: In mammals, daily rhythms of physiology and behavior are synchronized to the 24-hour light-dark (LD) cycle via retinal input to the suprachiasmatic nucleus (SCN), the master circadian clock. The SCN is divided into two subregions, the dorsomedial SCN (dmSCN) and ventrolateral SCN (vlSCN), and relies on a GABAergic coupling mechanism to maintain neural network synchrony. The SCN has been demonstrated to play an important role in sleep timing and quality. These aspects of sleep are frequently impaired in epilepsies, which are among the most common neurological disorders in the world. Previous work in our lab has characterized circadian behavior in a mouse model of epilepsy called Dravet syndrome (DS), which is caused by a loss-of-function mutation in the *Scn1a* gene coding for the pore-forming subunit of the $Na_V1.1$ sodium channel, found primarily in GABAergic interneurons. DS mice display circadian behavioral deficits including a longer endogenous period of activity and slowed entrainment to abrupt shifts in the LD cycle simulating jet lag. Additionally, ex vivo calcium imaging demonstrated impairment in intercellular communication between the vl- and dmSCN of DS mice. Based on these results, we predicted that DS mice would also display impaired circadian regulation of sleep. Here we present a model of jet lag in which we combine activity monitoring with electrocorticographic (ECoG) and electromyographic (EMG) recordings to assess circadian regulation of sleep-wake rhythms in DS and wild-type (WT) mice. Mice were first subjected to a 6-hour delay, followed by a 6-hour advance of the LD cycle, while ECoG/EMG data were recorded continuously for a month. We report that for both WT and DS mice, jet lag induces a transient misalignment in the circadian timing of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stages. For both genotypes, we also find differences in the kinetics of re-entrainment following jet lag between the primary bout of sleep and the “siesta”, an abbreviated sleep bout under control of the circadian clock. We hypothesize that differences in entrainment time between DS and WT mice are due to impaired intercellular communication between vl- and dmlSCN. Ongoing work is probing the role of the $Na_V1.1$ channel in the SCN in sleep timing and quality by knocking out the *Scn1a* gene in a region-specific manner. Our work contributes to the understanding of mechanisms underlying sleep disturbances in both epilepsy and jet lag, and provides a novel experimental paradigm for probing circadian sleep regulation in the mouse.

Disclosures: R.E. Sanchez: None. **I. Bussi:** None. **M. Ben-Hamo:** None. **H.O. de la Iglesia:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.02/UU5

Topic: F.08. Biological Rhythms and Sleep

Title: Sleep disturbance in the model rats of cerebrovascular dementia

Authors: *M. NAGAO[1], K. KUBOTA[2,1], S. KATSURABAYASHI[2], K. IWASAKI[2,1]
[1]Ins. Aging and Brain Sci., Fukuoka Univ., Fukuoka-Shi, Japan; [2]Fac. Pharmaceut. Sciences, Fukuoka Univ., Fukuoka-Shi, Japan

Abstract: The symptoms of patients with dementia are classified into core symptoms such as cognitive dysfunction and behavioral and psychological symptoms (BPSD) including sleep disturbance, anxiety, and depression. Sleep disturbance is known the main BPSD in the patients with light dementia. However, there is no specific insomnia drug for sleep disturbance in patients with dementia, because the mechanisms are still unknown. These facts may also be due to problem that there is no suitable animal model for sleep disturbance. We have previously reported that cerebral ischemia in rats showed significant impairments of spatial memory in the eight-arm radial maze task for a model of the cerebrovascular dementia. In the present study, we investigated whether cerebral ischemia rats show sleep disturbance by evaluating the sleep-wakefulness states. Cerebral ischemia was induced for 10 min by occluding both of the common carotid arteries, and this was repeated once after 1 hour. The rats were implanted with electrodes for electroencephalogram (EEG) and electromyogram (EMG) recording. Wakefulness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep were classified by an EEG/EMG recording during 24 hours 7 days after cerebral ischemia. The total time, average duration, number of episodes, and EEG power density of each wake/sleep state were computed during the light and dark phases. Cerebral ischemia rats significantly increased the total time of wakefulness and decreased the total time of NREM sleep during the light phase compared with sham-operated rats. However, the REM sleep was showed the no change. Furthermore, cerebral ischemia rats significantly decreased the average duration of NREM sleep and the number of NREM sleep episodes (more than 5 min), and increased the number of wakefulness episode (less than 5 min) during the light phase. However, the EEG power density of the delta (0.5 - 4.0 Hz) range in NREM sleep did not decrease in cerebral ischemia rats during the light phase. These results suggest that cerebral ischemia rats showed a decrease in the amount of NREM sleep and an increased number of awakenings without poor sleep efficiency. Therefore, we consider that cerebral ischemia rats would be an useful animal model for the new drugs especially remedying sleep disturbance in the patients with cerebrovascular dementia.

Disclosures: M. Nagao: None. **K. Kubota:** None. **S. Katsurabayashi:** None. **K. Iwasaki:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.03/UU6

Topic: F.08. Biological Rhythms and Sleep

Support: Department of Anesthesiology, University of Michigan

Title: Activation of basal forebrain cholinergic neurons reverses sevoflurane anesthesia and induces a wake-like state in rats

Authors: *J. DEAN[1], M. BRITO[2], T. LIU[3], A. FRYZEL[3], G. A. MASHOUR[3], D. PAL[3]
[1]Mol. and Integrative Physiol., Univ. of Michigan Dept. of Mol. and Integrative Physiol., Ann Arbor, MI; [2]Neurosci., [3]Anesthesiol., Univ. of Michigan, Ann Arbor, MI

Abstract: Recent work from our laboratory demonstrated that carbachol-mediated cholinergic stimulation of prefrontal cortex (PFC) increased local acetylcholine (ACh) levels and reversed general anesthesia [1]. PFC has reciprocal connections with cholinergic neurons in basal forebrain [2,3], which are known to increase activity during wakefulness [4,5]. Therefore, it is possible that cholinergic basal forebrain neurons were responsible for modulating arousal states and increasing cortical ACh levels after carbachol activation of PFC. To test this hypothesis, we conducted chemogenetic stimulation of basal forebrain cholinergic neurons in anesthetized rat. Under surgical anesthesia, male ChAT:Cre Long Evans rats (n=5) received bilateral microinjection (500nL) of AAV5:pAAV-hSyn-DIO-hM3D(Gq)-mCherry into substantia innominata region of the basal forebrain, and were instrumented to 1) record electroencephalogram (EEG) from across the cortex, 2) quantify local ACh levels through microdialysis, and 3) deliver Compound 21 [hM3D(Gq)-specific agonist] through a chronic catheter in jugular vein. After allowing five weeks for the maximal expression of hM3D(Gq), the rats were anesthetized with sevoflurane. General anesthesia was titrated (1.9-2.0%) to maintain loss of righting reflex (a surrogate of unconsciousness in rodents) and continuous slow wave EEG. Excitation of cholinergic basal forebrain neurons during sevoflurane anesthesia through intravenous administration of Compound 21 (5mg/kg) increased the respiration rate and caused EEG activation at a short latency (~10 s). The changes in respiration and EEG were accompanied by an increase in PFC ACh levels to those observed during pre-anesthesia baseline waking state. Importantly, all rats made active attempts at righting themselves and three out of five rats were able to fully right themselves despite continued presence of sevoflurane anesthesia. These results show that activation of cholinergic basal forebrain neurons is sufficient to reverse sevoflurane anesthesia in rats and induce a wake-like state.

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3. Briand et al. (2007) *Prog Neurobiol* 83, 69-91
4. Jones (2003) *Front in Biosci* 8, s438-451.
5. Xu et al. (2015) *Nat Neurosci* 18, 1641-1647.

Disclosures: J. Dean: None. **M. Brito:** None. **T. Liu:** None. **A. Fryzel:** None. **G.A. Mashour:** None. **D. Pal:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.04/UU7

Topic: F.08. Biological Rhythms and Sleep

Support: NSF CAREER 1565410 (IAM)

Title: Effects of sleep deprivation on memory and sleep patterns in young and aged adult mice

Authors: *M. R. LOPEZ[1], R. K. YUAN[2], M. C. GARAZA[1], A. GRENIER[1], V. R. CERDA[1], M. WOOD[1], C. M. GAGLIARDI[1], I. A. MUZZIO[1]
[1]Biol., Univ. of Texas At San Antonio, San Antonio, TX; [2]Harvard Med. Sch., Boston, MA

Abstract: Sleep is thought to play a key role in memory consolidation; however, the relationship between alterations in sleep patterns and memory remain elusive. Previous studies have shown that both cognition and sleep undergo several age-related changes. Here, we examined the effects of sleep deprivation on sleep patterns, hippocampal place activity, and memory in young and aged C57bl6 mice. All animals were trained in a hippocampus-dependent object-place recognition task. On day 1, mice were habituated to a novel environment in which they subsequently explored an array of 3 objects over the course of 3 consecutive training sessions. Immediately after the last training session, animals were sleep deprived (SD) for 5 hours using an automated sleep deprivation system. The following day, animals were reintroduced to the environment for a single test session in which one object was displaced. Sleep patterns were analyzed before sleep deprivation and during sleep recovery using a Bayesian algorithm method. Prior to the sleep deprivation session, old mice displayed more fragmented sleep in comparison to young mice, as previously reported in other studies. Following the SD session, both young and old SD mice exhibited a trend toward less time awake and increased time in NREM. Interestingly, old SD mice also displayed reduced number, but longer length NREM bouts compared to old controls, which indicated that NREM not increased but was also more consolidated. The changes in sleep patterns correlated with alterations in memory and cellular

representations. Young SD animals exhibited lower preference for the displaced object, along with less place cell remapping during the test session relative to controls. Surprisingly, these trends were reversed in aged adult mice, which exhibited enhanced memory of the moved object and place cell remapping during the test session, a phenotype similar to that observed in young control mice. These data suggest that age-related sleep fragmentation contributes to some of the cognitive deficits associated with aging. However, consolidation of NREM sleep serves to ameliorate these changes by facilitating memory retrieval and allowing representations in the hippocampus to adapt to changing environments.

Disclosures: M.R. Lopez: None. **R.K. Yuan:** None. **M.C. Garaza:** None. **A. Grenier:** None. **V.R. Cerda:** None. **M. Wood:** None. **C.M. Gagliardi:** None. **I.A. Muzzio:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.05/UU8

Topic: F.08. Biological Rhythms and Sleep

Support: NC123240.1

Title: Sleep and depressive-like behavior in rat: Differential effects between early life stress exposure and adulthood acute stress exposure

Authors: *A. VALDÉS-CRUZ, A. E. DÍAZ-FUENTES, M. G. MARTÍNEZ-MONTALVO, S. ESCALERA-OLVERA, S. ALMAZÁN-ALVARADO
Inst. Nacional de Psiquiatría RFM, México, Mexico

Abstract: Depressive disorder has different effects on sleep, as hypersomnia, insomnia, short duration of sleep stages, increase or reduction sleep latency, etc. Depression sleep disturbances could depend on factors such as depression onset age, and severity. In animal models, early life stress exposure by maternal separation and early social deprivation (MSESD) induce depressive-like behaviors that are present since childhood and are maintained to adult age. 15 minutes forced swimming is a method to induce depressive-like behaviors and has been considered a form to acute stress (AS), mainly when it is applied in adult age. Nevertheless, there is a controversy about depressive effect duration of this procedure. The aim of the present study was to compare the effect of MSESD and AS on depressive-like behaviors and on sleep architecture. Male Wistar rats were used. MSESD rats (n = 6) on postnatal day 21 were isolated from both their mother, and their littermates, also housed in an individual cage throughout all experiment. AS rats (n = 6) were housed in groups of three subjects until experimental procedure was started. In adulthood (postnatal day 85-95), all animals were implanted with electrodes in right and left hippocampus, both prefrontal cortices, and neck muscles to record the electromyogram. Four six-

hour polysomnographic records were done on consecutive days. On the second day, in AS group 15 minutes forced swimming was carried out. To quantify the depressive-like behavior 24 hours after forced swimming test (FST) 5 minutes duration was applied. In MSESD group solely FST was applied in the second day. In polysomnographic records the total time (TT) and number of phases (NP) of wakefulness, slow waves sleep (SWS) and rapid eye movement sleep (REM) stages were analyzed. In FST immobility, swimming, and climbing were analyzed. MSESD group showed lower TT in wakefulness ($p < .002$) and SWS ($p < .001$), and higher NP in SWS ($p < .01$) and REM ($p < .01$) than the AS group in the first record. Also in third record MSESD exhibited lower TT in SWS ($p < .001$) and higher NP in SWS ($p < .001$) and REM ($p < .03$). Repeated measures analysis showed that TT and NP in SWS of MSESD group were similar in the four polysomnographic records, while the AS group reach a similar level after the 15 minutes forced swimming and recovered in subsequent records. FST showed no difference between groups. Effects of the AS on sleep are transitory; only show impact in the stress exposition day. However, the results suggest a permanent effect of the MSESD on SWS and REM sleep, than could have a direct association with the expression of depressive-like behaviors.

Disclosures: A. Valdés-Cruz: None. **A.E. Díaz-Fuentes:** None. **M.G. Martínez-Montalvo:** None. **S. Escalera-Olvera:** None. **S. Almazán-Alvarado:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.06/UU9

Topic: F.08. Biological Rhythms and Sleep

Support: VA BLR&D IK2BX002531

Title: Comparison of sleep loss and recovery between binge cocaine and standard acute sleep deprivation

Authors: *T. E. BJORNESS[1], R. W. GREENE[2]
[1]Mental Hlth. Res., VA Med. Ctr. of North Texas, Dallas, TX; [2]Dept Psychiatry & Dept Neurosci., UTSW & VAMC, Dallas, TX

Abstract: As a psychostimulant, cocaine disrupts sleep under both active use and abstinence conditions with additional alterations in sleep stage composition. We have previously characterized the sleep/waking response in mice to several cocaine doses commonly used in addiction-related research. Here, we compare the sleep disruption and rebound recovery of standard acute sleep deprivation to binge cocaine administration. Adult male C57BL/6 mice were implanted with EEG and EMG electrodes. After recovery from surgical procedures, acclimation to the recording tethers, and baseline EEG and EMG collection, mice underwent

acute sleep deprivation or a binge cocaine protocol. Sleep deprivation consisted of 4 h of forced slow walking via a treadmill. For binge cocaine, animals first were exposed to the binge protocol (1 injection/h for 3 consecutive h) with saline (IP), followed by binge cocaine (15 mg/kg) the next day. Sleep deprivation and binge injections began at the start of the light phase. Mice receiving injections were weighed immediately prior to the first injection of the day each day. Sleep latency was increased compared to binge saline following both acute sleep deprivation and binge cocaine with a longer latency following SD, while REM latency was significantly longer following cocaine compared to sleep deprivation. At 4 h into the light cycle (i.e. within the sleep deprivation and binge administration time range) there was no difference in sleep time between baseline and binge saline or binge cocaine and sleep deprivation. Both sleep deprived and binge cocaine groups showed SWA rebound as defined as an increase in SWA from the same circadian time under baseline conditions, with slightly different time courses of recovery. At the end of the 24 h period, both sleep deprivation and binge cocaine groups showed a non-significant trend of decreased slow wave sleep slow wave energy suggesting that slow wave energy was not fully recovered during the 21 h post-injection or 20 h post-sleep deprivation period. Interestingly, mice that were sleep deprived showed a large increase in slow wave energy during waking suggesting that recovery from sleep deprivation alters both subsequent sleep and waking EEG activity. In sum, binge cocaine resulted in a similar loss of sleep time as acute sleep deprivation with REM sleep particularly effected. Additionally, the time course of SWA recovery was sharper following sleep deprivation, perhaps in part due to the increase SWA during waking. This increase in SWA during waking was likely not seen in binge cocaine animals due to high monoaminergic tone which would preclude SWA expression.

Disclosures: T.E. Bjorness: None. **R.W. Greene:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.07/UU10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Role of weekend recovery sleep in neurobehavioral deficits in chronic sleep deprivation paradigm of night shift work in mice

Authors: *S. SHIYANA[1,2], K. KONDEPUDI, 160014[3], M. BISHNOI[3], K. CHOPRA[2]
[1]Univ. Inst. of Pharmaceut. Sci., Panjab Univ., Chandigarh, India; [2]Univ. Inst. of Pharmaceut. Sci., Chandigarh, India; [3]Natl. Agri-Food Biotech. Inst., Mohali, India

Abstract: Methods
Female Laca mice of age 2-3 months, were chronically sleep deprived from 9:00 am to 5:00 pm from Monday to Friday using modified multiple platform method for 4 weeks as per the approval

from institutional animal ethic committee. The mice were grouped into three groups: control, sleep deprived without weekend recovery (SD) and sleep deprived with weekend recovery sleep (SD+R) having n=12 in each group. The protocol design mimicked the night shift work condition. The neurobehavioral deficits were assessed using open field test, actophotometer and hyperactivity scoring. Neurobiological changes were assessed with serum melatonin, cortisol, insulin, lipopolysaccharides (LPS) and C reactive protein (CRP) levels along with prospective physiological assessment of body weight and body temperature.

Results

Hyperlocomotion was depicted by increased ambulatory counts, rearing counts, number of line crossings in SD and SD+R group. The hyperactivity scoring indicated the pronounced stereotype behaviour in SD group. However, the stereotype was also seen in SD+R when tested immediately after sleep deprivation.

The serum melatonin and CRP levels were increased in SD group. Furthermore, there was significant decrease in blood glucose in both the groups. However, the serum insulin was increased in SD+R group only. The serum cortisol and LPS was not altered. Moreover, there was significant loss in body weight in SD group as compared to SD+R. The alterations in body temperature was more evident in SD group. These findings highlighted that the weekend recovery sleep plays role in neurobiological functions not in alleviating the mania like behavior.

Conclusion

Weekend recovery sleep is insufficient to counter the circadian insult induced by continuous night shifts during the weekdays. The study has implications for night shift workers.

Disclosures: S. Shiyana: None. **K. Kondepudi:** None. **M. Bishnoi:** None. **K. Chopra:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.08/UU11

Topic: F.08. Biological Rhythms and Sleep

Support: NSERC
CIHR

Title: Coupling arousal and motor behavior: A dopamine hypothalamic circuit

Authors: *J. J. FRAIGNE, S. K. PINTWALA, M. HAMIEH, J. H. PEEVER
Cell & Syst. Biol., Univ. of Toronto, Toronto, ON, Canada

Abstract: Motivated behaviors such as exploring, drinking and grooming only occur during wakefulness and therefore rely on the coordination of circuits that promote arousal and motor activity. We hypothesize that A11 dopamine cells play this role. These cells are specifically

active when arousal and motor behavior are coupled ($p<0.01$, ANOVA, n=6). Optogenetic activation of A11 dopamine neurons simultaneously triggers brain arousal and increases postural muscle tone ($p<0.01$, ANOVA, n=6), while optogenetic silencing of A11 cells produces behavioral and motor quiescence ($p<0.01$, ANOVA, n=8). Here, we used electrophysiology, optogenetics, genetically-assisted circuit mapping and behavioral assays to determine through which circuits the A11 dopamine cells operate to couple arousal state and motor activity. We showed that A11 dopamine neurons synapse on and directly activate hypothalamic orexin neurons. Optogenetic activation of A11 dopamine terminals in the orexin field promotes cortical arousal ($p<0.01$, n=5, t-test) without producing any motor behavior ($p=0.89$, n=5, t-test). Whereas, optogenetic activation of A11 dopamine terminals in the trigeminal motor pool engages movement ($p<0.01$, n=5, t-test) without causing cortical arousal. We propose that A11 dopamine cells form a control circuit that functions to couple arousal state and motor activity by directly connecting to and synchronizing the activity of hypothalamic orexin cells and motor neurons.

Disclosures: J.J. Fraigne: None. **S.K. Pintwala:** None. **M. Hamieh:** None. **J.H. Peever:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.09/UU12

Topic: F.08. Biological Rhythms and Sleep

Support: Human Frontier Science Program Fellowship LT000338/2017-L
NIH R01 MH102638
NIH R01 MH087592

Title: Adolescent sleep disruption induces long-lasting impairment in social novelty preference

Authors: *W.-J. BIAN, L. DE LECEA
Dept. of Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: Sleep takes one-third of our lives, yet its function is largely unknown. A large proportion (50~80%) of children with autism spectrum disorders (ASDs) were reported to have sleep problems, including delayed sleep onset, shortened sleep duration and fragmentation of sleep continuity, and a correlation has been found between sleep impairment and defects of social interaction, a core symptom of ASDs. However, the causal relationship between sleep disruption and social deficits as well as the underlying mechanisms have not yet been established but are likely to be critical for understanding the etiology of ASDs and for developing potential therapeutic means. Here we found that developmental sleep disruption in adolescent mice caused significantly reduced preference towards the socially novel conspecific in adulthood in the three-

chamber social interaction test without affecting the overall sociality. These social defects were persistent to at least 1 month after the initial test, suggesting the effects caused by adolescent sleep disruption are long-lasting. Interestingly, sleep disruption in the adulthood did not induce any social defects, indicating a critical period in adolescence during which sleep shapes social novelty preference. Dopaminergic (DA) neurons in the ventral tegmental area (VTA) and their projections to the prefrontal cortex (PFC) and nucleus accumbens (NAc) are important players in social reward processing and motivation, and they are active during waking but mostly silent during sleep. We found that in adolescent mice, over-excitation of the VTA DA neurons, specifically in the light phase when sleep mostly occurs, led to long-lasting social defects similar to those caused by sleep disruption. In contrast, developmental over-excitation of the DA neurons in the substantia nigra pars compacta (SNc) had no significant effect on social novelty preference. Collectively, these results suggest a critical role of adolescent sleep and normal activity level of VTA DA neurons in the developmental shaping of social novelty preference.

Disclosures: W. Bian: None. **L. de Lecea:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.10/UU13

Topic: F.08. Biological Rhythms and Sleep

Support: 5T32HL007609-29 (PHS) to CLG
8G12MD007602 (NIMH) to JCE
1SC1GM127260-01 (NIH) to JCE

Title: Sleep in mice resilient and susceptible to social defeat stress

Authors: C. L. GRAY, J. SANCHEZ, *J. EHLEN
Neurobio., Morehouse Sch. of Med., Atlanta, GA

Abstract: Sleep disorders are a pervasive feature of a wide variety of neuropsychiatric conditions, and social stress is known to cause or exacerbate both sleep and neuropsychiatric disorders. It is also known that persons with sleep disorders prior to trauma have increased susceptibility to PTSD. In order to understand this relationship between sleep and stress we have employed a mouse model wherein sustained social avoidance occurs following social defeat stress. Preliminary data from this model are the first to demonstrate that development of social avoidance can be predicted by differences in sleep regulation that exist before exposure to social stress. Furthermore, these data demonstrate that increased sleep occurring after social-defeat stress is associated with resilience to social avoidance. These findings prompted us to examine local field potentials in a brain region linked to both social defeat susceptibility and sleep, the

medial prefrontal cortex (mPFC). We hypothesized that in vivo differences in the response of mPFC neurons to sleep are responsible for differences in susceptibility to social avoidance. Detailed analysis of slow-wave sleep and waking sleep pressure indicate electrophysiological differences in sleep occurring in the mPFC of susceptible and resilient mice. This suggests that the mPFC is a neural locus where sleep alters behavioral responses to social defeat stress.

Disclosures: C.L. Gray: None. **J. Sanchez:** None. **J. Ehlen:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.11/UU14

Topic: F.08. Biological Rhythms and Sleep

Support: JSPS KAKENHI 18K14846
The Naito Foundation 2017

Title: Search for neural circuits of narcolepsy-cataplexy

Authors: *E. HASEGAWA[1], T. MAEJIMA[2], T. YOSHIDA[3], M. YOSHIOKA[3], M. YANAGISAWA[1], M. MIEDA[2], T. SAKURAI[1]
[1]Intl. Inst. For Integrative Sleep Medi, Tsukuba, Japan; [2]Univ. of Kanazawa, Kanazawa, Japan; [3]Hokkaido Univ., Sapporo, Japan

Abstract: Mice lacking orexin peptides, orexin neurons, or orexin receptors recapitulate human narcolepsy phenotypes, further highlighting a critical role for orexin signaling in the maintenance of wakefulness. However, although the lack of orexin signaling causes the sleep disorder narcolepsy, the precise neural mechanisms by which orexin neurons prevent narcolepsy remain unclear. In a previous study, we found that targeted restoration of orexin receptor expression in the dorsal raphe (DR) and in the locus coeruleus (LC) of mice lacking both of orexin receptors inhibited cataplexy and pathological fragmentation of wakefulness (i.e., sleepiness), respectively. These results suggested that DR serotonergic and LC noradrenergic neurons play differential roles in orexin neuron-dependent regulation of sleep/wakefulness. As a next step, we used optogenetic and chemogenetic approaches to demonstrate that DR serotonin neurons suppress cataplexy by reducing the activity of the basolateral/lateral amygdala that plays an important role in emotional processing, as consistent with the fact that strong emotion often triggers cataplexy. Our results suggest that the orexin neuron-DR serotonin neuron-amygdala pathway is a critical circuit for preventing cataplexy. Furthermore, we identified a neuronal pathway that induces cataplexy when activated by optogenetic manipulation. We will discuss the role of this pathway in emotional processing as well as in REM-related muscle atonia.

Disclosures: E. Hasegawa: None. **T. Maejima:** None. **T. Yoshida:** None. **M. Yoshioka:** None. **M. Yanagisawa:** None. **M. Mieda:** None. **T. Sakurai:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.12/UU15

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant 1R01NS096151
NIH Grant 1 R21NS101469

Title: Activity of Amygdala GABA neurons during cataplexy

Authors: Y. SUN[1], E. BENDELL[1], B. ZOU[1], C. BLANCO-CENTURION[1], S. LUO[1], A. VIDAL-ORTIZ[1], P. J. SHIROMANI[1,2], *M. LIU[1]
[1]Psychiatry and Behavioral Sci., Med. Univ. of SC, Charleston, SC; [2]Ralph H. Johnson VA Med. Ctr., Charleston, SC

Abstract: Cataplexy, a distinctive symptom of sleep disorder narcolepsy, is usually triggered by strong emotions. The central nucleus of the amygdala (CeA) has been implicated in emotions and the GABA neurons in the CeA could regulate cataplexy. However, the real-time neuronal dynamics of identified GABA neurons during cataplexy is not known. In this study, we use fiber photometry to record calcium transients as a proxy of the activity of CeA GABA neurons during cataplexy. We generated narcoleptic VGAT-ires-Cre mice (VGAT-Cre+/-/orexin-/-) and identified narcoleptic symptoms. AAV-DIO-GCaMP6S was microinjected into the CeA and 21 days later sleep and calcium transients in CeA GABA neurons were recorded. We found that 30.95% of the cataplexy episodes were preceded by a GABA neuron activation event, indicating that other neurons in the CeA may also trigger cataplexy. Cataplexy and calcium events increased when mice were exposed to palatable food or predator odor. Surprisingly, we found that about 79.31% of the sleep attack episodes, which is another symptom of narcolepsy distinct from cataplexy, were accompanied by a concurrent activation of CeA GABA neurons. These results are the first to implicate CeA GABA neurons in triggering or maintaining sleep attacks. The circuit involving cataplexy is partially understood. However, sleep attacks are a more debilitating symptom of narcolepsy but the circuit is not known. We suggest that loss of orexin destabilizes amygdala neurons to trigger both cataplexy and sleep attacks.

Disclosures: Y. Sun: None. **E. Bendell:** None. **B. Zou:** None. **C. Blanco-Centurion:** None. **S. Luo:** None. **A. Vidal-Ortiz:** None. **P.J. Shiromani:** None. **M. Liu:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.13/UU16

Topic: F.08. Biological Rhythms and Sleep

Title: Vigilance dynamics are translated by head nodding in a mouse model of drowsiness

Authors: *A. SHIN[1], J. WOO[2], J. KIM[1], D. KIM[1]
[1]Dept. of Biol. Sci., KAIST, Daejeon, Korea, Republic of; [2]Chungnam Techno Park, Cheonan, Korea, Republic of

Abstract: In the drowsy state, the wake and sleep drives compete to yield a dynamic fluctuation of vigilance. It has proven challenging to study the mechanisms underlying vigilance dynamics, in part because of the lack of a robust animal model. Here, we established a mouse model of drowsiness. In this model, mice are starved for 1 day and then allowed to overeat high-fat food (to promote sleep) while positioned in an open-field box (to promote vigilance). They fall into a long-lasting drowsy state, as reflected by repeated and open-eyed nodding of the head while in a standing position. Simultaneous recording of electroencephalogram (EEG) and neck electromyogram (EMG) readouts revealed that this drowsy state had multiple stages in terms of the relationship between the vigilance level and head movements: the delta oscillations decreased in power prior to the head-rising period and increased during the head-falling period. CaV3.1-knockout mice, which have reduced delta oscillations, had a longer head-falling period with no difference in head-up latency compared to wild-type mice. This suggests that their balance is shifted from sleep to wakefulness, likely due to their previously proposed decrease in sleep-promoting functions. Our findings indicate that delta oscillations play a dominant role in controlling vigilance dynamics during sleep/wake competition, and that our novel mouse model may be useful for studying drowsiness and related neurological disorders.

Disclosures: A. Shin: None. **J. Woo:** None. **J. Kim:** None. **D. Kim:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.14/UU17

Topic: F.08. Biological Rhythms and Sleep

Support: NIH grant NS091546

Title: Spatial, functional, and translational profiling of the brain during sleep/wake behavior

Authors: *Y. HAN[1], P. LUU[2], A. NADTOCHIY[3], T. V. TRUONG[4], S. E. FRASER[5], D. K. DICKMAN[6]
[1]Neurosci. Grad. Program, [2]Mol. and Computat. Biol., [3]Biol. Sci., [4]Translational Imaging Ctr., [5]Mol. & Computat. Biol., [6]Neurobio., USC, Los Angeles, CA

Abstract: Synapses and neural circuits must maintain a dynamic balance of electrical activity in order to stabilize brain functionality throughout life, yet still permit the plasticity necessary to form and consolidate new memories. This exquisite balancing act is hypothesized to require the homeostatic control of synaptic strength during sleep-wake behavior, where synaptic strengthening accumulated through experiential wake activity is systematically down regulated during sleep, and experiences are consolidated and integrated into stable, long-term memories. Using the Drosophila adult central nervous system, we investigate the gene *insomniac*, a ubiquitin ligase adaptor that was recently demonstrated to be required for proper sleep behavior and homeostasis. Our approach utilizes the development of two complementary technologies: 1) New probes to visualize calcium activity and active gene translation in *insomniac*-expressing neuronal cell types, and 2) Use of multi-photon light sheet and light field microscopy to image sleep-related adaptations to neural activity in *insomniac*-positive neurons at unprecedented resolution, speed, and 3-dimensional coverage. These technologies are leveraged to complete three objectives: 1) Spatial profiling of genetically defined neurons and glia in relation to *insomniac* expression in the adult fly nervous system; 2) Calcium imaging in *insomniac* neurons at rest and following sleep deprivation; and 3) Translational profiling of *insomniac* neurons at rest and following sleep deprivation. Our findings illuminate previously undefined populations of neurons potentially involved in the homeostatic control of sleep behavior and adaptations in these cell types in the context of sleep/wake activity.

Disclosures: Y. Han: None. **P. Luu:** None. **A. Nadtochiy:** None. **T.V. Truong:** None. **S.E. Fraser:** None. **D.K. Dickman:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.15/UU18

Topic: F.08. Biological Rhythms and Sleep

Support: Craig H. Neilsen Foundation
NIH/NIGMS Institutional Research and Academic Career Development Award, 5K12-GM000680-17

Title: Changes in sleep architecture, respiratory behavior, and indices of pain correlate after thoracic spinal cord contusion

Authors: *H. KLOEFKORN[1], S. IDLETT[2], M. HALDER[3], B. GOOLSBY[2], L. M. AIANI[2], N. P. PEDERSEN[4], S. HOCHMAN[5]
[1]Physiol., [2]Emory Univ., Atlanta, GA; [3]Emory Univ., Alpharetta, GA; [4]Neurol., Emory Univ., Atlanta, GA; [5]Dept Physiol, Emory Univ. Sch. Med., Atlanta, GA

Abstract: Spinal cord injury (SCI) patients often experience disrupted sleep and chronic pain, and autonomic dysfunction[4], however these relationships are not well understood. In this study, we explored the relationship between sleep architecture, respiratory behavior, evoked secondary hyperalgesia, and spontaneous afferent population firing in a mouse model T10 contusion SCI. Prior to injury, measures of sleep architecture, resting respiratory behavior, and hind paw mechanical sensitivity were measured twice weekly in 11 female adult c57/bl6 mice for two weeks. Sleep architecture and resting respiratory behavior were measured using non-contact electric field sensors. These sensors have been validated against whole body plethysmography to reliably capture resting respiratory rate[2] and validated against electroencephalogram to measure sleep architecture from changes in respiratory behavior. Mechanical sensitivity of both hind paws was measured using von Frey filaments[1]. SCI was modeled in 7 mice using a moderate T10 contusion SCI (50 kDyne impact) with the remaining 4 serving as naïve controls. After 6 weeks following SCI, animals were euthanized and *in vitro* electrophysiologic recordings of spontaneous afferent population activity were obtained from isolated lumbar dorsal root ganglia (DRG) similar to previous work in rats correlating this increased firing to spontaneous pain[3]. Data were analyzed using 1-way ANOVAs and Tukey's post-hoc test for significance. Linear regressions were calculated to assess correlation between data.
Relative to baseline, SCI animals after 6 weeks developed 1) fragmented sleep behavior (reduced sleep event duration, $p=0.012$), 2) erratic breathing behavior (increased respiratory rate variability, $p=0.035$), 3) heightened mechanical sensitivity (evoked allodynia, $p<0.001$), and 4) increased spontaneous afferent population firing rate ($p=0.041$). Mechanical sensitivity correlated with both erratic breathing ($p<0.001$, $R^2=0.88$) and fragmented sleep ($p=0.016$, $R^2=0.64$). Fragmented sleep also correlated with afferent firing rate ($p=0.029$, $R^2=0.0.57$) and nearly with erratic breathing ($p=0.051$, $R^2=0.0.49$).
In summary, strong correlations between indices of pain, poor sleep quality, and erratic breathing were found after SCI. This is the first study, to our knowledge, to explore these relationships in SCI and further studies are planned to identify the neuroplasticity and causality between these measures.
1. Chaplan, S. R. *J. Neurosci. Methods* 53:55-63, 1994.2. Noble, D. J. *J. Neurosci. Methods* 277:88-100, 2016.3. Yang, Q. *J. Neurosci.* 34:10765-10769, 2014.4. Zambotti, M. *Neurosci. Biobehav. Rev.* 90:84-103, 2018

Disclosures: H. Kloefkorn: None. **S. Idlett:** None. **M. Halder:** None. **B. Goolsby:** None. **L.M. Aiani:** None. **N.P. Pedersen:** None. **S. Hochman:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.16/UU19

Topic: F.08. Biological Rhythms and Sleep

Support: NRF-2017R1A2B3011098
NRF-2014M3A7B4051596
NRF-2017M3C7A1023471
IBS-R026-D1
N0001720
Brain Korea 21 (BK21) PLUS program

Title: The Role of corticothalamic input in sleep regulation

Authors: *J. HONG, E. CHEONG
Yonsei Univ., Seoul, Korea, Republic of

Abstract: Sleep-wake control has been attributed to many brain regions, including the brain stem, hypothalamus, basal forebrain, basal ganglia, and thalamus. Sleep is composed of the non-rapid eye movement (NREM) and rapid eye movement (REM) sleep states, which are categorized by characteristic brain rhythms in electroencephalography (EEG) recordings and distinctive eye movements. The transition from wakefulness to a NREM sleep state at the onset of sleep involves a transition from low-voltage, high-frequency irregular EEG waveforms to large-amplitude, low-frequency EEG waveforms accompanying synchronized oscillatory activity in the thalamocortical circuit. The thalamocortical circuit consists of reciprocal connections between the thalamus and cortex. The thalamus is further dissected into thalamic reticular nuclei (TRN), which are composed of inhibitory neurons, and thalamocortical (TC) nuclei composed of excitatory neurons which reciprocally project each other. TC neurons send long axons to cortical neurons, and the cortical neurons in layer VI send strong excitatory feedback back to both TRN and TC neurons, which completes the loop of thalamocortical circuit. Within this circuit, the cortex sends strong excitatory feedback to the thalamus, however the function of which is unclear. In this study, I investigated the role of corticothalamic input to TC neurons in sleep architecture and sleep rhythms using genetically targeted inhibition of TC neuron in response to corticothalamic inputs.

Disclosures: J. Hong: None. **E. Cheong:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.17/UU20

Topic: F.08. Biological Rhythms and Sleep

Support: Wellcome Trust Studentship 109059/Z/15/Z
Clarendon Fund
Sleep and Circadian Neuroscience Institute
University of Oxford

Title: The roles of sleep oscillations in sensory and memory processing: New insights using transgenic and auditory stimulation approaches in mice

Authors: *C. BLANCO DUQUE[1], R. PURPLE[2], T. YAMAGATA[2], G. ANG[1], L. E. MCKILLOP[1], M. M. KAHN[1], D. M. BANNERMAN[3], V. V. VYAZOVSKIY[1]
[1]Dept. of Physiology, Anat. and Genet., [2]Sleep and Circadian Neurosci. Institute, Nuffield Dept. of Clin. Neurosciences, [3]Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Spindles are oscillations (10-15 Hz) occurring during NREM sleep, which have been implicated in sensory processing and memory consolidation. Deficits in spindles have been reported in brain disorders associated with alterations in the GluA1 AMPA receptor subunit, which is encoded by the GRIA1 gene. Here, we investigate the role of spindles in sensory gating and memory processing in mice using transgenic and sensory stimulation approaches. First, we investigated the effect of knocking-out the GRIA1 gene in mice on local spindle properties, and studied the association between these oscillations and memory performance. Chronic in-vivo electroencephalography (EEG), electromyography (EMG), local-field potentials (LFP) and multi-unit activity (MUA) recordings from the primary somatosensory cortex (S1) were collected in GRIA1$^{-/-}$ (n=6) and wild-type (WT) littermates (n=6) male mice during both natural sleep and training on a spatial reference memory task. Frontal EEG spectral power during NREM sleep was significantly reduced in the spindle-frequency range (10-15 Hz) in GRIA1$^{-/-}$ relative to WT mice ($p<0.05$). Furthermore, individual EEG spindle events were readily detected in WT mice with an automated algorithm, while they were absent in GRIA1$^{-/-}$ mice ($p<0.05$). Interestingly, despite the absence of EEG spindles in GRIA1$^{-/-}$ mice, analyses of LFP signals revealed an occurrence of local spindle events in the S1 in both genotypes ($p>0.05$). A repeated measures analysis revealed significant learning across training (main effect of day; $F(6,36)=17.01, p<0.001$). However, there was no significant difference between genotypes in memory performance (main effect of genotype and interaction by day; $F<1; p>0.20$). This is consistent with previous evidence indicating that long-term memory formation is preserved in GRIA1$^{-/-}$ mice. Second, we assessed whether auditory stimuli could modulate spindles. In vivo

EEG, EMG, LFP and MUA recordings were collected in GRIA1$^{-/-}$ (n=4) and WT (n=4) male mice, over 24-hour periods, during both spontaneous sleep and sensory stimulation. Auditory stimuli appeared to disrupt sleep spindles and reduce MUA in local areas within S1 where spindles were especially prominent. This reduced MUA faded with repetitive presentation of acoustic stimuli in WT but not GRIA1$^{-/-}$ mice, consistent with earlier observations associating GluA1 deletion with impairments in habituation. These results have important implications for understanding the spatio-temporal dynamics and function of cortical spindles. More generally, our study provides novel insights into the biological role of sleep oscillations in sensory and memory processing.

Disclosures: R. Purple: None. **T. Yamagata:** None. **G. Ang:** None. **L.E. McKillop:** None. **M.M. Kahn:** None. **D.M. Bannerman:** None. **V.V. Vyazovskiy:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.18/UU21

Topic: F.08. Biological Rhythms and Sleep

Support: HHMI

Title: Control of non-REM sleep by a thalamo-amygdala circuit

Authors: *C. MA, S. AN, Z. K. BARGER, W.-C. CHANG, D.-Q. LIU, Y. DAN
Dept. of Mol. and Cell Biol., UC Berkeley, Berkeley, CA

Abstract: A crucial step in understanding the neural circuits controlling sleep is to identify the sleep neurons. In principle, a neuron could promote sleep by inhibiting wake-promoting neurons or by exciting other sleep-promoting neurons. Based on this simple logic, we performed anatomical screening for candidate sleep neurons followed by functional validation of the candidates. Rabies virus (RV)-mediated retrograde trans-synaptic tracing identified a subpopulation of neurons in the central nucleus of the amygdala (CeA) as a major source of GABAergic inputs to multiple wake-promoting neuronal populations. Optogenetic activation of these CeA neurons strongly promoted non-REM (NREM) sleep and suppressed both wakefulness and REM sleep, whereas their inactivation had the opposite effects. Optrode recording showed that the vast majority of these neurons are maximally active during NREM sleep. Furthermore, RV-mediated retrograde tracing from these CeA neurons revealed inputs from a subgroup of glutamatergic neurons in a posterior region of the thalamus. Optogenetic activation and inactivation of these thalamic neurons also increased and decreased NREM sleep, respectively. Together, these results reveal a novel thalamo-amygdala pathway for NREM sleep generation.

Disclosures: C. Ma: None. **S. An:** None. **Z.K. Barger:** None. **W. Chang:** None. **D. Liu:** None. **Y. Dan:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.19/UU22

Topic: F.08. Biological Rhythms and Sleep

Support: G170382516 from the Collaborative Health Initiative Research Program (CHIRP) at the Uniformed Services University of the Health Sciences

Title: A mouse model of neuroinflammation resulting from sleep disruption at high altitude

Authors: *N. P. CRAMER[1], A. GRILLAKIS[2], X. XU[1], Y. EUDY[1], K. WHITING[2], Z. GALDZICKI[1]
[1]Anatomy, Physiol. and Genet., [2]Grad. Program in Neurosci., Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Hypobaric hypoxia experienced by travelers at high altitude can cause significant disruptions to normal sleep. In turn, prolonged sleep disruptions promote systemic inflammation including elevation of proinflammatory cytokines which may interact with those driven by prolonged exposure to hypoxia to synergistically drive neuroinflammation. We developed a mouse model of sleep disruption under high altitude conditions to determine the mechanisms underlying the resulting neuroinflammation and associated behavioral deficits. Mice were group housed at sea level or a simulated altitude of 5000 meters for three weeks followed by two weeks of either normal or fragmented sleep. Sleep fragmentation occurred at the respective altitudes and consisted of a bar which swept across the bottom of the cage every two minutes during the light cycle. Mice exposed to high altitude showed significant deficits in contextual and cued fear conditioning relative to sea level controls and these deficits tended to be more severe in mice which underwent additional sleep fragmentation at altitude. Peripheral blood cytokine profiles show elevated levels of IL-6 in mice which underwent sleep fragmentation regardless of altitude exposure. EEG/EMG analysis is ongoing to determine which components of sleep (NREM/REM) may be more affected by either altitude or sleep fragmentation. These results will help elucidate the mechanisms underlying neuroinflammation resulting from sleep disruption under hypobaric-hypoxia and potential interventions to prevent or minimize long-term neurological consequences.

Disclosures: N.P. Cramer: None. **A. Grillakis:** None. **X. Xu:** None. **Y. Eudy:** None. **K. Whiting:** None. **Z. Galdzicki:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.20/VV1

Topic: F.08. Biological Rhythms and Sleep

Support: 1 R01 NS 102209

Title: Acute kynurenine challenge reduces rapid eye movement (REM) sleep duration and impairs hippocampal-dependent contextual memory in adult male and female rats

Authors: *S. A. BUCK[1], A. BARATTA[1], S. BEGGIATO[3], J. A. MONG[2], A. POCIVAVSEK[1]
[1]Maryland Psychiatric Res. Center, Dept. of Psychiatry, [2]Univ. of Maryland Sch. of Med., Baltimore, MD; [3]Life Sci. and Biotech., Univ. of Ferrara, Ferrara, Italy

Abstract: Increases in kynurenic acid (KYNA), a metabolite of the kynurenine pathway of tryptophan degradation and an antagonist at N-methyl-D-aspartate (NMDA) and α7 nicotinic acetylcholine (α7nACh) receptors in the brain, impair cognitive function. Recent evidence suggests that these disruptions may be causally related to impairments in sleep-wake behavior with KYNA elevation. Presently, we further explored the novel hypothesis that elevated KYNA adversely impacts sleep quality and cognition in adult cohorts of both male and female Wistar rats. Animals were treated with either vehicle or kynurenine (100mg/kg; intraperitoneally), the direct precursor to KYNA, at the beginning of the light cycle, zeitgeiber time (ZT) 0, or at the beginning of the dark cycle, ZT 12. *In vivo* microdialysis confirmed significant formation of KYNA in the dorsal hippocampus with kynurenine challenge at both time points. Separate animals were implanted with telemetric devices to acquire polysomnographic recordings that combine electroencephalogram (EEG) and electromyogram (EMG). Analysis of vigilance state-related parameters categorized as wake, rapid eye movement (REM) and non-REM (NREM) were assessed for 24 h after treatment. Kynurenine treatment at ZT 0 significantly reduced REM duration compared to vehicle treatment ($P < 0.05$), and we also found a main effect of sex ($P < 0.01$). Alternatively, when animals were treated at ZT 12, REM duration was impacted by a significant treatment x sex interaction ($P < 0.05$), but no main effect of treatment alone. Separate animals were tested in the passive avoidance paradigm, assessing contextual memory. Animals were treated with vehicle or kynurenine at ZT 0 or ZT 12 and trained in the task at ZT 2 or ZT 14, respectively. The next day, during the retention trials, animals treated with kynurenine at the start of the light phase were significantly impaired in the hippocampal-dependent task ($P < 0.05$), whereas animals challenged with kynurenine at the start of the dark phase were not impaired. Taken together, these findings and future complementary experiments will provide significant mechanistic value to understanding the role of KYNA in modulating a relationship between sleep and cognition.

Disclosures: S.A. Buck: None. **A. Baratta:** None. **S. Beggiato:** None. **J.A. Mong:** None. **A. Pocivavsek:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.21/VV2

Topic: F.08. Biological Rhythms and Sleep

Support: Ministero della Salute "Grant Finalizzata"

Title: Modulation of startle response in rem sleep behavior disorder

Authors: *R. FRAU, F. TRACCIS, M. FIGORILLI, M. PULIGHEDDU
Univ. of Cagliari, Cagliari, Italy

Abstract: REM sleep behavior disorder (RBD) is a parasomnia featuring loss of normal muscle atonia, vivid dreams and complex behaviors during REM sleep. Patients with idiopathic RBD are susceptible to develop neurodegenerative diseases such as Parkinson's disease (PD). About 50% of PD patients exhibit RBD, typically in association with higher severity of PD symptoms, and increased risk for neuropsychiatric problems. RBD results from imbalances of excitatory and inhibitory inputs across several brainstem areas, such as the sublaterodorsal tegmental nucleus (SLD), medullary gigantocellular reticular nuclei and laterodorsal-pedunculopontine complex (LTD-PPN). Interestingly, the same structures are involved in the execution and modulation of startle reflex, a defensive response consisting in muscular contraction in reaction to sudden sensory stimuli. Here, we tested whether the alterations of REM sleep induced by lesions of the key areas involved in RBD pathogenesis (including SLD and LTD-PPN) were paralleled by (and correlated to) abnormalities of startle reflex and its modulatory processes in rat models. Adult Sprague-dawley rats were subjected to electrolytical lesions of SLD and LTD/PPN, or sham surgery and implanted with electrodes for 24-hour polysomnography (PSG) testing. Rats were then tested for either PSG or startle reflex paradigms, including startle habituation and pre-pulse inhibition (PPI). Our preliminary results showed that the lesion of SLD and LTD-PPN significantly reduced startle amplitude and habituation, but not PPI. Furthermore, animals subjected to LTD/PPN lesion exhibited more robust startle alterations than SLD and these alterations were accompanied by sleep behavioral abnormalities. Our results suggest that specific startle alterations in association with sleep disorders may provide a complementary early diagnostic index in PD development.

Disclosures: R. Frau: None. **F. Traccis:** None. **M. Figorilli:** None. **M. Puligheddu:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.22/VV3

Topic: F.08. Biological Rhythms and Sleep

Support: DA041180

Title: Activation of adenosine monophosphate-activated protein kinase (AMPK) and sleep deprivation induced phenotypes

Authors: *D. EACRET[1,2], S. JIN[3], S. F. KIM[3,4], M. T. MANNERS[2], S. C. VEASEY[5], J. A. BLENDY[2]
[2]Systems Pharmacol. and Translational Therapeut., [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Div. of Endocrinology, Diabetes, and Metabolism, Dept. of Med., [4]Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [5]Ctr. for Sleep and Circadian Neurobio., Univ. of Pennsylvania, Perelman Sch. of Med., Philadelphia, PA

Abstract: Depression is a debilitating disorder that is a major economic and public health burden. First line antidepressants are only 40-50% effective, and require weeks of treatment before patients respond. Most depressed patients have disrupted sleep, yet one night of total sleep deprivation paradoxically has robust and rapid antidepressant properties. Sleep deprivation is an effective therapy for up to 60% of patients who experience antidepressant effects within hours following the night of sleep deprivation. This antidepressant response is lost after one night of recovery sleep, thus sleep deprivation cannot be adopted as a long-term treatment strategy. Understanding and exploiting the mechanisms underlying the fast and effective antidepressant response to sleep deprivation could lead to novel therapeutics to treat depression. Adenosine Monophosphate-activated Protein Kinase (AMPK) is the major energy sensor in the brain and is phosphorylated following sleep deprivation as well as by other rapid acting antidepressants such as ketamine. We used two methods of sleep deprivation to investigate the role of pAMPK in mediating antidepressant effects of sleep deprivation. Male and female mice were exposed to either spontaneous exploratory wakefulness or gentle handling for 6 hours. The gentle handling method of sleep deprivation increased corticosterone levels compared with spontaneous exploratory wakefulness and non-sleep deprived controls. Our preliminary data indicate an increase pAMPK in the spontaneous exploratory wakefulness paradigm in the hippocampus of males but not females, although a downstream target of AMPK, nuclear Sterol Regulatory Element-Binding protein (nSREBP), was increased in females. Female mice did not show an antidepressant response to acute sleep deprivation in the forced swim test (FST). However, sleep deprivation as an antidepressant therapy is only effective in depressed humans. Therefore, future

studies will use 12 days of chronic unpredictable stress, to further investigate the extent to which AMPK is necessary for a rapid antidepressant effect after sleep deprivation.

Disclosures: D. Eacret: None. **S. Jin:** None. **S.F. Kim:** None. **M.T. Manners:** None. **S.C. Veasey:** None. **J.A. Blendy:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.23/VV4

Topic: F.08. Biological Rhythms and Sleep

Title: SUVN-G3031, H3 receptor inverse agonist produces wake promoting activity in rats with hypocretin-2-saporin lesions of the lateral hypothalamus

Authors: *S. DARIPELLI, G. BHAYRAPUNENI, C. TIRUMALASETTY, V. BENADE, R. SUBRAMANIAN, S. PETLU, N. PRAVEENA, P. JAYARAJAN, A. SHINDE, R. BADANGE, V. BHATTA, R. NIROGI
DMPK, Suven Life Sci. Ltd, Hyderabad, India

Abstract: Numerous studies have demonstrated that brain histamine plays a crucial role in maintenance of wakefulness, attention, learning and other cognitive processes. SUVN-G3031, a potent H3 receptor inverse agonist is being developed for the treatment of narcolepsy and other sleep related disorders. SUVN-G3031 is one of the lead molecules with hKi of 8.7 nM and has more than 100 fold selectivity against the related GPCRs. SUVN-G3031 exhibited desired pharmacokinetic properties and brain penetration. SUVN-G3031 blocked R-α-methylhistamine induced water intake and increased *tele*-methylhistamine levels in brain and cerebrospinal fluid. A single oral administration of SUVN-G3031 produced significant increase in acetylcholine, histamine, dopamine and norepinephrine levels in the cortex. SUVN-G3031 produced wake promoting activity in male Wistar rats. In the present study, effects of SUVN-G3031 on sleep/ wake profile were evaluated in rats with lateral hypothalamic lesion using neurotoxin hypocretin-2-saporin. Narcoleptic-like sleep behavior was observed in rats injected with hypocretin-2-saporin in lateral hypothalamus. SUVN-G3031 produced significant increase in wakefulness with concomitant decrease in rapid eye movement (REM) sleep in these animals. These results are in agreement with electroencephalography (EEG) studies carried out in healthy male Wistar rats. Results from the current study and the neurotransmitter modulations produced by SUVN-G3031 provide a strong basis for the potential of SUVN-G3031 in treatment of sleep related disorders. First in human, Phase 1 studies for SUVN-G3031 are completed underUS IND and SUVN-G3031 has shown desirable pharmacokinetic profile with safety and tolerability in healthy human volunteers. Phase 2 study for narcolepsy is currently being planned.

Disclosures: **S. Daripelli:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **G. Bhayrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **C. Tirumalasetty:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Petlu:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Praveena:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Badange:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Bhatta:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.24/DP10/VV5

Topic: F.08. Biological Rhythms and Sleep

Support: NIH/NINDS Grant R44NS083218
Kentucky Cabinet for Economic Development Grant KSTC-184-512-13-158
Higher Committee for Education in Iraq scholarship to A. Ajwad

Title: Validation of a sensory feedback system for selective sleep restriction in rodents

Authors: D. M. HUFFMAN[1], A. A. AJWAD[1], A. AGARWAL[4], B. F. O'HARA[2], K. D. DONOHUE[3], *S. SUNDERAM[1]
[1]Dept. of Biomed. Engin., [2]Dept. of Biol., [3]Dept. of Electrical & Computer Engin., Univ. of Kentucky, Lexington, KY; [4]Signal Solutions, LLC, Lexington, KY

Abstract: Sleep plays a vital role in physiological and homeostatic processes, with each state of sleep (Rapid Eye Movement (REM), non-REM (NREM)) mediating unique aspects of learning, memory, and cognition. A common approach to investigating these state-specific contributions is by restricting the state in question and observing the consequences. However, experimental tools to identify and selectively interrupt sleep are still underdeveloped: most are stressful to the animal, infringe on normal behavior, or are open-loop in operation. To this end, we sought to accomplish the common goal of REM Sleep Restriction (RSR) by means of automated, non-invasive vibro-tactile stimulation, which was applied via a tactile transducer mounted under the floor of the cage (MouseQwake; Signal Solutions, LLC.), and could be activated with predetermined stimulation parameters (frequency/amplitude) to yield more subtle or intense intervention. Eight C57BL/6 mice (4M, 4F) were instrumented with EEG/EMG headmounts

according to IACUC-approved protocols. Following recovery, signals were fed into an unsupervised computational model which predicted vigilance state in real time, and triggered stimulation upon detecting REM sleep. Each animal underwent four trials (each using a unique frequency/amplitude combination), which consisted a 12-hour baseline, as well as a time-locked 12-hour trial of RSR (stimulation triggered when REM detected) on the following day. Data was then manually scored by human raters, and the effect of stimulation on REM sleep was assessed. While more subtle stimulation showed no clear effect, more intense stimulation drastically affected REM sleep - reducing mean REM bout duration by 50-70% depending on stimulation parameters. The overall proportion of REM sleep was also reduced by as much as 40% during the first 4 hours of RSR, which eventually led to a homeostatic rebound to compensate for lost REM. In conclusion, this system provides a non-invasive alternative to currently available systems for sleep restriction in rodents. The stimulation parameters can be tuned to suit a particular animal or experimental condition, and can be adapted to compensate for persisting sleep resulting from homeostatic- or circadian-dependent changes in arousal thresholds. Future work is directed toward automated selection of stimulation parameters, and the incorporation of non-invasive sensors to alleviate the need for surgical implantation of EEG/EMG. These improvements will result in a completely non-invasive system that could be implemented with limited or no experience in surgical methods or sleep scoring and analysis.

Disclosures: D.M. Huffman: None. **A.A. Ajwad:** None. **A. Agarwal:** None. **B.F. O'Hara:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signal Solutions, LLC. **K.D. Donohue:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signal Solutions, LLC. **S. Sunderam:** 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.; Signal Solutions, LLC.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.25/VV6

Topic: F.08. Biological Rhythms and Sleep

Support: JSPS Kakenhi 17H04754

Title: A new method for recording rodents' physical activity using an implantable accelerometer

Authors: D. FUNABASHI, I. KITA, *T. NISHIJIMA
Tokyo Metropolitan Univ., Tokyo, Japan

Abstract: [Background] Physical activity is a key to sustaining physiological and mental health. However, population worldwide are increasingly becoming physically inactive. To overcome the physical inactivity-related health problems, it would be important to understand neural mechanisms that regulate physical activity level in rodents. So far, home-cage activity of rodents is usually examined in a single housed condition, because the recording apparatuses based on a beam-interruption, a telemetry, and a video-tracking system require animal isolation. Here, it would be notable that social isolation is a type of stress and has been demonstrated to affect emotional behaviors, impair spatial learning, and suppress hippocampal neurogenesis in rodents. Obviously, home-cage activity of rodents should be recorded in a group housed condition, which is feasible by using an implantable accelerometer, nanotag® (15 × 14.2 × 7.1 mm, 2.5 g, Kissei Comtec Ltd, Japan). [Purpose] As the first step, the purpose of this study was to examine a validity of the nanotag® in mice, i.e., whether an intraperitoneal implantation of nanotag® do not decrease home-cage activity and impair hippocampal neurogenesis. [Methods] Male C57BL6J mice (10 weeks old) were randomly allocated to following three groups; control (C, n = 5), sham-operated (SO, n = 5), and operated mice (O, n = 6). In this experiment, we needed to record the home-cage activity of C and SO mice that were not received nanotag® implantation, all the mice were singly housed, and their home-cage activities were recorded by a near infrared beam interruption system (LOCOMO LS-5, Melquest, Japan). Twenty-three days after the nanotag® implantation, mice were deeply anesthetized and the brain were removed for immunohistochemical examination of hippocampal neurogenesis (cell proliferation by Ki-67, and immature neuron by doublecortin). [Results and Discussion] Home-cage activities of both O and SO mice were transiently decreased due to the surgical invation for a few days, but no significant differences were observed between groups at 7 days after operation. We also found that there were no significant differences in densities of Ki-67-positive cells and of doublecortin-positive immature neurons between groups. [Conclusion] Theses results suggest that the intraperitoneal implantation of nanotag® do not influence ambulatory activity and hippocampal neurogenesis in mice. This device enables us recording physical activity of group-housed mice in any environmental situation.

Disclosures: D. Funabashi: None. **I. Kita:** None. **T. Nishijima:** None.

Poster

679. Biological Rhythms and Sleep: Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 679.26/VV7

Topic: F.08. Biological Rhythms and Sleep

Support: ANR-1 1-IDEX-0007
PEPS EXOMOD 2015-2016

Title: ONEIROS, a new telemetric and logger device to record sleep electrophysiology, physiology, temperatures, behavior, arousal threshold and sleep homeostasis

Authors: *P.-A. LIBOUREL[1], S. ARTHAUD[1], B. BARRILLOT[1], J. ROUX[1], G. UNGUREAN[2,1], P.-H. LUPPI[1], C. PEYRON[1], N. C. RATTENBORG[2], B. MASSOT[3]
[1]CRNL, Lyon, France; [2]Avian Sleep Group, Max Planck Inst. for Ornithology, Seewiesen, Germany; [3]INL, UMR5270 CNRS, INSA Lyon, Villeurbanne, France

Abstract: Sleep is a behaviorally inactive state of reduced environmental awareness shared by all animals. When compared to wakefulness, sleep behavior is associated with changes in physiology and activity of the central nervous system. The nature of these changes varies considerably across species, and therefore is a rich resource for gaining insight into the evolution and functions of sleep. A major obstacle for capitalizing on this resource is the lack of a small device capable of recording a high number of biological parameters for extended periods of time both in the laboratory and the field. We developed ONEIROS to this aim. This new tool is designed for sleep research on small freely moving animals. The system is a standalone, miniature, long-lasting (several days) that couples electrophysiological (up to 26 electroencephalogram (EEG), electromyogram (EMG), electrooculogram (EOG), electrocardiogram (ECG) and/or local field potentials (LFPs) channels), metabolic (3 temperature channels), and behavioral measurements (3D accelerometry). In addition, the device is equipped with a lightweight vibrating motor which can be used to assess arousal thresholds and to disrupt sleep. The system is available in a wireless or a datalogger configuration useable in the field. To demonstrate the efficacy of this tool, we simultaneously recorded for the first time, EEG, hippocampal LFP, electromyogram (EMG), electrooculogram (EOG), brain, body and ambient temperature, and 3D accelerometry. Moreover, we performed a selective paradoxical sleep deprivation by triggering the vibrating motor after online recognition of the state. Finally, we successfully recorded a pigeon (*Columbia livia*) in an 8 meters cube aviary in a social context with the logger mode, demonstrating the feasibility of using the device in the field.

Disclosures: **P. Libourel:** F. Consulting Fees (e.g., advisory boards); Viewpoint SA. **S. Arthaud:** None. **B. Barrillot:** None. **J. Roux:** None. **G. Ungurean:** None. **P. Luppi:** None. **C. Peyron:** None. **N.C. Rattenborg:** None. **B. Massot:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.01/VV8

Topic: F.10. Food Intake and Energy Balance

Support: PICTO-GLAXO 2013-0065
CONICET

CIC

Title: Ghrelin signaling targets segregated clusters of neurons within the nucleus of the solitary tract

Authors: *M. P. CORNEJO[1], P. N. DE FRANCESCO[1], G. GARCIA ROMERO[1], E. PORTIANSKY[2], J. M. ZIGMAN[3], M. REYNALDO[1], M. PERELLO[1]
[1]IMBICE, La Plata, Argentina; [2]Sch. of Vet. Sci., LAI, La Plata, Argentina; [3]Intrnl. Med. and Psychiatry, Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Ghrelin is a stomach-derived peptide hormone and its receptor, the growth hormone secretagogue receptor (GHSR) is highly expressed in the brain. The nucleus of the solitary tract (NTS) is a major sensory nucleus in the dorsal medulla that receives cardiovascular, visceral, gustatory and orotactile information. NTS neurons express GHSR but the identity and the physiological role of GHSR-expressing neurons of the NTS are uncertain. In this study, we used a GHSR reporter mouse (GHSR-eGFP) to perform a detailed neuroanatomical and functional characterization of GHSR-expressing neurons of the NTS. We first mapped the neuroanatomical distribution of eGFP neurons within the NTS. Then, we explored the phenotype of eGFP neurons using IHC against different neuronal populations. We also explored the physiological role of GHSR-expressing neurons of the NTS exposing GHSR-eGFP animals to experimental protocols known to activate the NTS and to involve ghrelin signaling and examining the pattern of expression of c-Fos in eGFP positive cells. Overall, we found that GHSR-expressing neurons were located throughout the extension of the NTS forming three clusters: one pair of rostral clusters, mostly comprising the ventral subnucleus, and one caudal cluster, mostly involving the parvicellular subnucleus. We also found that a population of GHSR-expressing neurons is GABAergic. Finally, eGFP neurons of the rostral clusters of the NTS showed an increase in c-Fos in response to hyperphagic protocols, while the caudal cluster of eGFP cells increased c-Fos levels in response to sensory stimuli from the gastrointestinal tract. Our results indicate that ghrelin signaling targets segregated clusters of NTS neurons that respond to different stimuli depending on their location.

Disclosures: M.P. Cornejo: None. **P.N. De Francesco:** None. **G. Garcia Romero:** None. **E. Portiansky:** None. **J.M. Zigman:** None. **M. Reynaldo:** None. **M. Perello:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.02/VV9

Topic: F.10. Food Intake and Energy Balance

Support: NINDS NS101616

Title: The minor spliceosome is required for proper hypothalamic development resulting in overeating and obesity in U11 cKO mice

Authors: *A. WHITE, K. C. HYATT, R. KANADIA
Physiol. and Neurobio., Univ. of Connecticut, Storrs, CT

Abstract: In mammals, feeding is regulated by the neuroendocrine system, atop which sits the hypothalamus, which not only integrates these signals but also actively regulates feeding behavior. The hypothalamus develops from the Nkx2.1 progenitor population of the ventral diencephalon. Proper hypothalamic development relies upon controlled production of neuronal subtypes and the ratio of these subtypes is determined by regulated gene expression. Here we explore the role of minor intron splicing in hypothalamic development. The minor spliceosome is comprised of 5 small nuclear RNAs (snRNAs) U11, U12, U5, U4atac, and U6atac and is responsible for the splicing of minor introns, which are present in ~500 genes, called minor intron-containing genes (MIGs). Despite being responsible for the splicing of less than 0.5% of introns, mutations in components of the minor spliceosome have been implicated in developmental disorders including MOPD1 and IGHD. Here we use *Nkx2.1*-cre to ablate *Rnu11*, which encodes the U11 snRNA, a crucial component of the minor spliceosome, whose loss results in perturbed minor spliceosome function in the developing hypothalamus. Upon birth, U11-null *Nkx2.1-cre+* mice are indistinguishable from control littermates. However, these mice upon shifting to *ad libitum* food at P21, while underweight, begin gaining weight such that they became obese. Weight gain analysis showed that the females surpass their littermates' weight by 5 weeks and males by 8 weeks. Body composition analysis, shows a significant shift in the lean-to-fat mass ratio, preceding the adult-onset obesity in the mutant mice. Together these findings show the influence of minor spliceosome in hypothalamic development and its effect on adult-onset obesity.

Disclosures: A. White: None. **K.C. Hyatt:** None. **R. Kanadia:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.03/DP11/VV10

Topic: F.10. Food Intake and Energy Balance

Support: ADA Pathway 1-17-INI-15
NIH DK020572

Title: Pacap from the ventromedial hypothalamic nucleus is necessary for both energy balance and glucose homeostasis

Authors: *J. N. FLAK[1], B. LOWELL[2,4], R. A. ROSS[3,4,5]
[1]MEND, Univ. of Michigan, Ann Arbor, MI; [3]Psychiatry, [2]Beth Israel Deaconess Med. Ctr., Boston, MA; [4]Harvard Univ., Boston, MA; [5]McLean Hosp., Belmont, MA

Abstract: Obesity results from energy imbalance, due, at least in part, to suppressed energy expenditure. While it is understood that the brain controls energy expenditure, the neurocircuits, and essential components within these circuits, that can accelerate and decelerate energy consumption have not yet been revealed in great detail. The ventromedial hypothalamic nucleus (VMN) is a critical neural site for the control of energy expenditure. While the VMN contains, almost exclusively, glutamatergic neurons, neuropeptides are also expressed within the nucleus. Pituitary adenylate cyclase activating polypeptide (pacap) is the most abundant neuropeptide in the VMN. Since previous studies have implicated pacap^{VMN} in controlling metabolic tone in response to energy status, we hypothesized that pacap^{VMN} is necessary for body weight regulation by promoting energy expenditure. We acquired a pacap^{flox} mice that, in the presence of cre, results in a truncated protein, preventing communication downstream by pacap. Because pacap is expressed in the periphery, we administered a local injection of AAV^{cre} into the VMN of pacap^{flox} mice. Bilateral AAV^{cre} administration completely ablated dmVMN *pacap* expression. We found that, in both male and female mice, loss of pacap^{VMN} results in massive obesity, adiposity, and hyperglycemia. Surprisingly, food intake only increased in these mice once body weight had almost doubled. In support of this notion, pacap^{VMN}KO suppressed VO2 and not activity, despite massive obesity. Together, these data indicate that pacap^{VMN} is necessary for the control of energy expenditure. In addition to the control of energy balance, Pacap^{VMN}KO also induced hyperinsulinemia and suppressed glucose clearance to brown adipose tissue, heart, and muscle during hyperinsulinemic/euglycemic clamp. Our data demonstrate that pacap is an essential component for the promotion of energy expenditure by the VMN. Future studies will reveal both the VMN cells that use pacap for these functions and the downstream cells necessary for the control of energy balance and glucose homeostasis.

Disclosures: J.N. Flak: 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.; Novo Nordisk. **B. Lowell:** None. **R.A. Ross:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.04/VV11

Topic: F.10. Food Intake and Energy Balance

Title: Acute exposure to a high fat diet during the juvenile period: Effects on cognition and post translational modifications in adulthood

Authors: *T. M. MILEWSKI[1], K. A. BUCKHAULTS[2], A. J. LARA[3], P. T. ORR[2,1], K. A. STUMPO[3]
[1]Neurosci. Program, [2]Psychology Dept., [3]Chem. Dept., Univ. of Scranton, Scranton, PA

Abstract: Obesity is a worldwide epidemic and is closely related to diet-induced diabetes. Diabetes and hypoglycemia brought on by a high fat diet interfere with memory in human and mice as well as induce post-translational modifications such as phosphorylation and glycosylation of certain proteins, but little is known about these effects during the juvenile period. During this study, mice were exposure to a high fat diet (HFD) for eight weeks starting at 24 days postnatal. Mice receiving the HFD did not weigh significantly more prior to exposure ($t(11) = .954$, $p = .36$), but were significantly heavier at 3 ($t(11) = 2.61$, $p = .024$) and 6 weeks ($t(11) = 4.803$, $p = .001$). During the sixth week of exposure, behavioral testing began. Mice were tested on rotarod, open field, and Morris Water Maze to investigate motor coordination, anxiety, and memory. Motor coordination was assessed by a two day rotarod test. Mice exposed to HFD during the juvenile period spent significantly less time on the rod during day one ($F(1,10) = 11.473$, $p = .007$) and day two ($F(1,11) = 15.095$, $p = .003$) when compared to control mice. In general, mice in both groups did not demonstrate learning in the Morris Water maze. Additionally, there was no difference between groups on performance on day two ($F(1, 10) = 2.337$, $p = .157$) of testing. However, HFD mice took significantly more efficient paths to the platform on day three ($F(1,11) = 9.756$, $p = .01$). Moreover, mice exposed to the HFD did not display significantly more thigmotaxis of the open field ($t(11) = 1.214$, $p = .25$). Subsequent to behavioral testing, brain samples were taken for analysis of phosphorylation and glycosylation patterns induced by the HFD. Overall, these preliminary data suggest that juvenile exposure to HFD can affect motor behavior but may not affect learning or anxiety. Further, these exposures may result in differential post-translational modifications.

Disclosures: K.A. Buckhaults: None. **A.J. Lara:** None. **P.T. Orr:** None. **K.A. Stumpo:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.05/VV12

Topic: F.10. Food Intake and Energy Balance

Support: PAPIIT IN307417

Title: Binge eating induction does not modify sensitivity to the reinforcing properties of sucrose

Authors: *W. ZEPEDA-RUIZ[1], D. N. VELÁZQUEZ-MARTÍNEZ[2]
[1]Univ. Nacional Autonoma De Mexico, Mexico, Mexico; [2]Psicofisiología, Univ. Nacional Autónoma de México, Mexico City, Mexico

Abstract: Binge eating behavior is characterized by overconsumption of palatable food during brief periods of time in absence of energy deficits. It has been suggested that subjects with binge eating behavior assign a greater incentive value to food and that this is reflected in the amount of work that subjects is able do to obtain the palatable food; according to this view, Wojnicki *et al*. (2010) reported that after inducing binge, his subjects achieved higher break points when vegetable shortening was employed as reinforcer. However, we were unable to see an increase in the breaking points of a progressive ratio schedule after binge induction with sucrose. We thought that through training the constant exposure to sucrose during the operant session may induce a reduction of the reinforcing properties of sucrose. Therefore, the objective of the present experiment was to evaluate the performance of subjects with binge eating behavior in a progressive ratio schedule, employing different sucrose solutions as reinforcer. Twelve male Wistar rats (250-300 g) were trained in a progressive ratio schedule, after achieving behavioral stability (no more than 15% of variability in the break point during the last ten sessions); thereafter, subjects were divided according to their break point in two groups: control and experimental, and binge eating induction started following the protocol described by Corwin *et al*. (2006). Both groups had *ad libitum* access to water and standard food; access to a 10% sucrose solution was continuous for the control group and restricted (2 h per day, three days a week) to the experimental group. After binge induction, subject's performance was evaluated in the progressive ratio schedule, employing as reinforcer three sucrose solutions (5.62%, 10% y 17.78%) that were presented in a counterbalanced way. We found that subjects of control and experimental group decreased their break point after binge eating induction. Furthermore, all subjects achieved higher break points with the 17.78% sucrose solution and lowest break points with the 5.62% sucrose solution than with the training concentration of 10%. These results suggest that binge induction do not alter the reinforcing effects of sucrose or the subject's ability to discriminate between different sucrose solutions.

Disclosures: W. Zepeda-Ruiz: None. **D.N. Velázquez-Martínez:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.06/VV13

Topic: F.10. Food Intake and Energy Balance

Support: NIH (NIDDK): DK104897
Institutional Start-up funds (LAS)

NSF GRFP

Title: Juvenile and adolescent acesulfame potassium consumption induces hippocampal-dependent learning deficits and anxiety in young adulthood

Authors: *L. TSAN[1,2], V. W. LEE[1], L. A. SCHIER[3], S. E. KANOSKI[3]
[2]Neurosci. Grad. Program, [3]Dept. of Integrative and Evolutionary Biol., [1]USC, Los Angeles, CA

Abstract: Non-nutritive artificial sweeteners (NAS) have become increasingly common in an attempt to maintain the taste of sweetness while reducing carbohydrate and overall caloric intake. Given that consumption of NASs has increased by nearly 200% in children over the past 20 years, it important to understand the extent to which exposure to these substances during critical periods of development in early life affects neurocognitive function. The present study tested the hypothesis that consumption of three common NAS—acesulfame potassium (AceK), stevia, or saccharin—during the juvenile and adolescent periods (postnatal day 26-77) influences cognitive outcomes in rats when tested during young adulthood. Importantly, NAS ingestion was limited to the FDA's acceptable daily intake range (based on mg/kg/day). Our results revealed that consumption of AceK, but not stevia or saccharin, impaired spatial memory in the Barnes maze and increased anxiety-like behavior in the zero maze relative to controls. Overall, these results suggest that early life daily consumption of AceK during the juvenile and adolescent periods of development produces hippocampal-dependent memory deficits and elevated anxiety-like behavior in male rats. Moreover, these neurocognitive outcomes appear to be specific to AceK and do not generalize to other commonly used NASs.

Disclosures: L. Tsan: None. **V.W. Lee:** None. **L.A. Schier:** None. **S.E. Kanoski:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.07/VV14

Topic: F.10. Food Intake and Energy Balance

Support: Korea Research Foundation

Title: Early exposure to high fat diet affects feeding related behavior

Authors: *H. SONG, M. KIM, H. CHOI
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: The prevalence of obesity has increased and it is well known that obesity can cause many health problems. Moreover, the consumption of the palatable foods like high-fat diet (HFD) can cause obesity. Also, exposure to over nutrition environment leads to not only alter the

metabolism but also the mental state. Previous studies has reported that the maternal HFD can increase the risk of being obesity in offspring. However, the effect of eating HFD during childhood and adolescent is not well studied in the perspective of the behavior. We hypothesized that early exposure to the palatable foods after weaning state may cause obesity and modulate neuronal developmental process to increase feeding behavior. We measured the food-reward behavior by three tests : operant conditioning test (motivation level for appetitive pellet), conditioned place preference test (CPP) using palatable food, and three chamber test using social cue and food cue. Locomotive function and anxiety was tested using open field test. Memory function was tested using novel object recognition test. Locomotive function and anxiety was not significantly different between control diet group and HFD group. HFD mice showed significantly decreased motivation level for appetitive pellet compared with control group. HFD mice significantly drank less sucrose water compared with control group. When both control group and HFD group was combined, motivation level for appetitive pellet was in inverse correlation with bodyweight. These results suggest that early exposure to high fat diet may affect neural circuits and feeding related behavior.

Disclosures: H. Song: None. **M. Kim:** None. **H. Choi:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.08/VV15

Topic: F.10. Food Intake and Energy Balance

Support: NRF 2016R1C1B2007319
NRF 2017M3C7A1043845
NRF 2016R1A4A1010796
KHIDI HI17C2665

Title: Genetic dissection of a lateral septum circuit that regulates feeding behavior

Authors: *K. KIM, H.-E. PARK, J. PARK, S.-Y. KIM
Inst. of Mol. Biol. and Genet., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Feeding, a fundamental behavior of animals, underlies homeostatic control of energy balance by providing caloric input. Although neural mechanisms controlling feeding behavior is extensively studied in hypothalamic regions, emerging evidences suggest that feeding behavior is regulated in complicated manner by multiple, redundant circuits innervating various brain regions. A recent study revealed the role of the septal complex in feeding behavior. However, specific cell population in the septal complex contributing to food consumption is not established yet. Here, by monitoring *in vivo* calcium dynamics and optogenetically stimulating lateral

septum neurons, we show that a subpopulation of GABAergic neurons in the caudal lateral septum are related to regulation of feeding behavior. We found that the septal GABA neurons are acutely inhibited upon food intake, whereas optogenetic stimulation of the same neurons showed trends towards decreased caloric consumption only in starved animals. Based on these preliminary data, we are investigating the structure and function of the septal neurons and their projections in feeding behavior.

Disclosures: K. Kim: None. **H. Park:** None. **J. Park:** None. **S. Kim:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.09/VV16

Topic: F.10. Food Intake and Energy Balance

Support: Work supported by the European Union and co-financed by the European Social Fund (grant agreement no. EFOP-3.6.2- 16-2017-00012, project title: Development of a product chain model for functional, healthy and safe foods from farm to fork and also by the grant agreement no. EFOP-3.6.3-VEKOP-16-2017-00005, project title: „Strengthening the scientific replacement by supporting the academic workshops and programs of students, developing a mentoring process)"
BR was also supported by the János Bolyai Research Fellowship of the Hungarian Academy of Sciences

Title: The subtle effects of dietary glucose and fructose on the ultrastructure of the hippocampus

Authors: *G. M. MARCELLO[1], E. ANDRÁSOFSZKY[2], V. E. MARKEVICIUS[1], P. SOTONYI[1], J. Z. SZABO[2], B. RACZ[1]
[1]Dept. of Anat. and Histology, [2]Dept. of Animal Nutr., Univ. of Vet. Med. Budapest, Budapest, Hungary

Abstract: The brain's resolute need for sugar elicits exploration of the effects of different carbohydrate sources on cognitive function. Increased fructose intake is of particular interest in light of increasing public awareness of obesity. Consumption of sustained high amounts of high fructose corn syrup in industrially processed foods and beverages has supported interweaving metabolic and neurological effects on human health. Short-term (8 weeks) of increased fructose versus glucose or starch intake as the sole carbohydrate source was investigated for its influence on well-documented hippocampal synaptic organization. Quantitative electron microscopy of CA1 stratum radiatum with a subsequent series of morphological measurements of synaptic profiles sheds light on the post-synaptic functional effect of fructose on hippocampal synapse structure. Surprisingly, increased fructose consumption in Wistar rats was found not to have a

notable impact on post-synaptic ultrastructure in the hippocampus. Differences in morphological measurements of spines in fructose feeding rats, except for spine size between fructose and starch treatment groups, were found to be not significant as compared to glucose or starch test group values. As compared to glucose and starch, fructose did not show significant ultrastructural changes in CA1 spines. Fructose was found to have a negligible influence on hippocampus-dependent synaptic plasticity.

Disclosures: G.M. Marcello: None. **E. Andrásofszky:** None. **V.E. Markevicius:** None. **P. Sotonyi:** None. **J.Z. Szabo:** None. **B. Racz:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.10/VV17

Topic: F.10. Food Intake and Energy Balance

Support: DA037566

Title: Nicotinic acetylcholine receptors in the arcuate nucleus and their implications for feeding behavior

Authors: *C. A. CALARCO[1], Z. LI[3], S. R. TAYLOR[4], S. LEE[5], W. ZHOU[2], J. FRIEDMAN[6], Y. S. MINEUR[7], C. GOTTI[9], M. PICCIOTTO[8]
[1]Psychiatry, [2]Yale Univ., New Haven, CT; [3]The Rockefellar Univ., New York, NY; [4]Neurobio. Section, Biol. Sci., UCSD, La Jolla, CA; [5]Univ. of Chicago, Chicago, IL; [6]Rockefeller Univ/ HHMI, New York, NY; [7]Psychiatry, [8]Dept Pyschiat, Yale Univ. Sch. Med., New Haven, CT; [9]CNR, Neurosci. Inst., Milano, Italy

Abstract: Despite the known health risks associated with smoking, up to 20% of the US population persist in this behavior. Many individuals smoke to control their weight or are resistant to quitting due to fear of post-cessation weight gain. In clinical populations, nicotine and tobacco use is associated with lower body weight, and cessation yields an average weight gain of about 10 lbs, mostly within the first year. In rodent models, nicotine reduces weight gain, reduces food consumption, and alters energy expenditure, but these effects vary with duration and route of nicotine administration. Nicotine, acting through nicotinic acetylcholine receptors (nAChRs), increases the firing rate of both orexigenic agouti-related peptide (AgRP) and anorexigenic pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (ARC), however, it is unknown exactly how this yields reduced food intake.
The subunit composition of nAChRs directly controls their regulation of neuronal excitability, and while it has been shown that the β4 subunit is expressed on POMC neurons in the ARC, it was not known whether this expression is selectively expressed in anorexogenic neurons or how

other nAChR subtypes are distributed in this nucleus. Using translating ribosome affinity purification (TRAP) on ARC tissue from mice with ribosomes tagged in either AgRP or POMC cells, we examined nAChR subunit mRNA levels using real-time PCR. Further, we used immunoprecipitation to probe the subunit composition of functionally assembled nAChR. Numerous common and rare nAChR subtypes are expressed in the ARC, and there are fewer differences in expression between AgRP and POMC neurons than previously hypothesized. Further, the functional nAChR in this region are unique with respect to other brain areas that express the β4 subunit.
AgRP and POMC neurons have opposing functions with respect to controlling food intake, yet these cells are anatomically intermingled within the ARC. Cell type selective virally-delivered small hairpin RNAs targeting either the β4 or α7 subunit were used to examine the contribution of each subunit in either AgRP or POMC cells to the behavioral response to nicotine. While β4 and α7 subunits have different roles in the ARC with respect to responding to the nicotinic drugs nicotine and cytisine, their roles in AgRP and POMC cells are not dramatically different, despite the different functions of these cell populations.
Taken together these experiments further inform our understanding of nAChR signaling in the ARC and provide the basis for a new hypothesis regarding the regulation of this circuit by nicotinic drugs.

Disclosures: C.A. Calarco: None. **Z. Li:** None. **S.R. Taylor:** None. **S. Lee:** None. **W. Zhou:** None. **J. Friedman:** None. **Y.S. Mineur:** None. **C. Gotti:** None. **M. Picciotto:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.11/VV18

Topic: F.10. Food Intake and Energy Balance

Support: NIH/NCI grant (RO1CA207287)

Title: A new intracellular emetic signaling system: The pivotal role of Glycogen Synthase Kinase 3 (GSK-3) in vomiting evoked by a variety of emetogens in the least shrew (Cryptotis parva)

Authors: *W. ZHONG, N. DARMANI
Western Univ. of Hlth. Sci., Pomona, CA

Abstract: GSK-3, is a mutifunctional kinase and is involved in a variety of diseases. Its two isoforms GSK-3alpha and GSK-3beta are both constitutively active and upon cellular stimuli turns into its catalytic inactivation by phosphorylation at ser 21 and 9. To investigate the role of GSK-3 in emesis, we examined GSK-3α/β phosphorylation at Ser21/9 via performing Western

blots on brainstem protein extracts from least shrews treated intraperitoneally with fully effective emetic doses of diverse emetogens such as selective and/or nonselective agonists of serotonergic 5-HT3 (e.g. 5-HT or 2-Me-5-HT, 5 mg/kg)-, tachykinin NK1 (e.g. GR73632, 5 mg/kg)-, dopamine D2 (e.g. apomorphine or quinpirole, 2 mg/kg)-, cholinergic M1 (e.g. McN-A343, 2 mg/kg)-receptors, the L-type calcium channel agonist (FPL 64176, 10 mg/kg), chemotherapeutics thapsigargin (0.5 mg/kg, 0.5 mg/kg). Brainstems were collected at multiple time points post emetogens administration. The increase of GSK-3α/β phosphorylation at Ser21/9 was observed following administration of all above discussed emetogens. The increase located in brainstem emetic nuclei (the dorsal vagal complex) was further confirmed through immunostaining brainstem sections of FPL64176-treated least shrews. Moreover, GSK-3 inhibitor SB216763 at a low dose 0.25 mg/kg exerted potent and broad-spectrum antiemetic efficacy against vomiting in response to fully efficacious doses of discussed emetogens. Our findings demonstrate a pivotal role for GSK-3 in vomiting and implies targeting signals up and/or downstream of GSK-3 enzyme may provide powerful new avenues for developing new and potent antiemetics.

Disclosures: W. Zhong: None. **N. Darmani:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.12/VV19

Topic: F.10. Food Intake and Energy Balance

Support: PAPIIT IN307417

Title: A model of binge eating with solid palatable food

Authors: *S. ORTEGA-TINOCO[1], W. A. ZEPEDA-RUIZ[2], D. N. VELÁZQUEZ-MARTÍNEZ[2]
[1]Fisiología, UNAM, Ciudad de Mexico, Mexico; [2]Psicofisiología, Facultad de Psicología, Mexico City, Mexico

Abstract: Binge eating behavior is characterized by overconsumption of palatable food in brief periods of time without energy deficits. Several animal models had been suggested to study the characteristics of this eating disorder, but the most employed is the limited access model (Corwin et al., 2004, *Appetite,*139-142*)*, on which subjects have restricted access to palatable food (vegetable shortening or sucrose) 3 times a week. But humans have more varied diets, therefore, we evaluate the binge eating induction employing a solid food (M&M´s) with a high content of fat and sugar following Corwin et al. (2006) protocol. Twenty-four male Wistar rats were assigned to a control or experimental (according to their body weight) group; both groups had

continuous access to standard food and water. Control group had unrestricted access to M&M´s while the experimental group had access only two hours per day three days a week. After 4 weeks on this food schedule, clear (and significant) differences emerged between the groups. Furthermore, subjects did not change their water or standard food intake and the body weight of both groups increased along the manipulation; such results suggest that is possible to induce binge using M&M´s as palatable food. Additionally, in future studies, the use of food that resembles the complexity of human diet could contribute to evaluate the simultaneous effect of fats and carbohydrates in the reward system.

Disclosures: S. Ortega-Tinoco: None. **W.A. Zepeda-Ruiz:** None. **D.N. Velázquez-Martínez:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.13/VV20

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant DP1MH103908

Title: Functional characterization of a parabrachial microcircuit underlying satiety

Authors: *E. RODRIGUEZ, D. RYU, F. WANG
Neurobio., Duke Univ., Durham, NC

Abstract: Organisms consume nutritious food to maintain metabolic homeostasis and continue their survival. Evidence has shown that there are extrinsic and intrinsic processes, relayed via intricate neural circuitry, orchestrating the initiation and termination of food consumption, such as appetite and satiety. More specifically, there are functionally distinct neural circuits mediating both forms of homeostatic and aversive satiety. Although neural circuitry underlying aversive satiety is well characterized, the circuitry underlying homeostatic satiety is not fully understood. Interestingly, various appetite and satiety signaling nodes project directly onto a distinct caudal sub-region of the lateral parabrachial nucleus (PB_L), which is a node which regulates various emotional and visceral processes including both homeostatic and aversive satiety. Using a novel activity-dependent neuronal labeling technology called CANE, we identified and selectively labeled condensed milk (CM)-activated caudal lateral PB_L (PB_{cl}) neurons that are not $CGRP^+$. We further performed various behavioral assays. Optogenetic activation of these satiety-PB_{cl} neurons induced place preference and decreased CM consumption, whereas silencing increased CM consumption. The novel satiety-PB_{cl} circuit revealed here demonstrates a neural substrate for homeostatic satiation.

Disclosures: E. Rodriguez: None. **D. Ryu:** None. **F. Wang:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.14/VV21

Topic: F.10. Food Intake and Energy Balance

Title: Nucleus accumbens projections to the ventral tegmental area mediate primary reward behavior

Authors: C. BOND, R. TRINKO, E. FOSCUE, *R. J. DILEONE
Psychiatry, Yale Univ. Sch. Med., New Haven, CT

Abstract: The nucleus accumbens (NAc) is a basal ganglia structure critically important for reward learning, drug addiction and ingestive behavior. Recent work has described the synaptic targets of NAc (shell) projections in the ventral tegmental area (VTA), and demonstrated the role of this pathway in drug seeking behaviors. We sought to determine the activity and function of accumbal VTA projections in natural reward seeking. Using viral anterograde tracing, we find robust projections from the dopamine receptor 1 (D1) medial NAc neurons to both dopamine and non-dopamine cells in the ventral VTA. Optogenetic activation of this pathway reduced food intake and seeking, without affecting motivation or valence state. To assess the activity of VTA-projecting NAc neurons during intake, we selectively labeled this pathway using a viral strategy with retrograde Cre injected into the VTA, and Cre-dependent GCaMP6s into the NAc. Calcium transients were monitored during operant food seeking via fiber photometry. Consistent with optogenetic manipulations, we find that VTA projecting MSNs are modulated during both food seeking and food receipt. Together, these anatomical, functional, and activity experiments demonstrate that NAc projections to the VTA are important for primary reward seeking and consumption.

Disclosures: C. Bond: None. **R. Trinko:** None. **E. Foscue:** None. **R.J. DiLeone:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.15/VV22

Topic: F.10. Food Intake and Energy Balance

Support: NSF Grant IOS-1656626 (CAG)
VA Grant 121 BX002085 (LPR)
VA Grant IO1 BX001804 (LPR)

Title: Leptin-sensitive raphe neurons send projections to hypothalamic nuclei

Authors: *N. D. MAXWELL[1], L. P. REAGAN[1,2], J. R. FADEL[1], F. Z. LOYO-ROSADO[1], C. A. GRILLO[1,2]
[1]Pharmacology, Physiol. & Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC; [2]WJB Dorn VA Med. Ctr., Columbia, SC

Abstract: Leptin is an adipocyte hormone that controls a myriad of homeostatic functions. Most notably, leptin acts on neurons in the hypothalamus through the JAK/STAT pathway to control energy homeostasis and appetite. Leptin has not only been shown to act on hypothalamic neurons, but also on other select areas of the brain such as the raphe nuclei, the primary source of serotonin (5-HT) in the brain. Given the well described effects of 5-HT on feeding, we are interested in studying the connections between the raphe and the hypothalamic nuclei. Although, these connections have been described anatomically, their functional roles remain to be elucidated. We hypothesized that there are leptin-sensitive serotonergic neurons in the raphe nuclei that send projections to different nuclei within the hypothalamus including the arcuate. Our objectives are (1) to define raphe neurons sensitive to leptin that send projections to the hypothalamic nuclei and (2) to verify whether these neurons are serotonergic or not. Accordingly, we bilaterally injected fluorescently tagged cholera toxin-subunit-B (fCTB, a retrograde tracer) into the arcuate nucleus of adult male sprague-dawley rats. One month following the tracer administration, the rats were injected with leptin into the lateral ventricle and perfused with paraformaldehyde 1 hour later. Immunohistochemistry and immunofluorescence were performed on these brain sections, primarily focusing on the raphe nucleus. In order to observe colocalization between our targets, we triple-labeled with antibodies against phosphorylated STAT3 (pSTAT3), a marker for leptin activated neurons, and tryptophan hydroxylase (TPH), a marker of 5-HT neurons along with the fCTB from the injection into the arcuate. Our immunohistochemical results showed that fCTB was co-localized with TPH in the raphe nucleus, indicating that serotonergic neurons project to the arcuate nucleus. More importantly, we observed that serotonergic and non-serotonergic raphe neurons that project to the arcuate nucleus are activated by leptin, showing pSTAT3 staining in response to the leptin injection. These data support our hypothesis that there is an existing leptin-mediated raphe pathway projecting to the hypothalamus. Moving forward, we aim to better understand this pathway and the role that it may play in energy homeostasis and appetite regulation. Additionally, we will further characterize projections to other hypothalamic nuclei that may be important in appetite regulation, as well as determining the other non-serotonergic neuronal subtypes that may play a role within this system.

Disclosures: N.D. Maxwell: None. **L.P. Reagan:** None. **J.R. Fadel:** None. **F.Z. Loyo-Rosado:** None. **C.A. Grillo:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.16/WW1

Topic: F.10. Food Intake and Energy Balance

Title: Genetic mapping of central glucose sensing circuits

Authors: *S.-B. YANG
Inst. of Biomed. Sci., Academia Sinica, Taipei, Taiwan

Abstract: Diabetes is one of the epidemic diseases in the world. Multiple organs are involved in the pathophysiological development of diabetes, including brain. To ensure a constant supply of energy source, primarily glucose, to the brain, some neurons in the hypothalamus receives peripheral information such as nutrient and hormones and adjust gluconeogenesis and insulin sensitivities a variety of peripheral tissues, including liver and muscles. Previous *in vivo* multi-electrode recording and *ex vivo* brain slice patch clamp recording studies have shown that some neurons are reside within the dorsomedial hypothalamus (DMH), ventromedial hypothalamus (VMH), the arcuate nucleus (ARC) and lateral hypothalamus (LH) are sensitive to glucose. Biochemical studies further revealed that those glucose-sensing neurons express prerequisite molecules such as glucose transporters, glucokinase and certain ion channels that enable them to tune their excitability at different glucose levels. Nevertheless, the physiological effects upon direct manipulating these glucose-sensitive neurons are still largely unknown and the roles of these glucose-sensitive neurons in the metabolic syndrome remain elusive. In this study, we combine mouse genetics and electrophysiology to establish the causal relationship between the activity of this glucose-sensing neural ensemble and the physiological states.

Disclosures: S. Yang: None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.17/WW2

Topic: F.10. Food Intake and Energy Balance

Support: NIH R00 MH097792
NIH R01 MH112739

IBACS Seed Grant

Title: Single cell transcriptomic analysis of the lateral hypothalamic area reveals molecularly distinct populations of inhibitory and excitatory neurons

Authors: L. E. MICKELSEN[1], M. BOLISETTY[2], B. R. CHIMILESKI[1], A. FUJITA[1], P. ROBSON[2], *A. C. JACKSON[1]
[1]Physiol. and Neurobio., Univ. of Connecticut, Storrs Mansfield, CT; [2]The Jackson Lab. for Genomic Med., Farmington, CT

Abstract: The lateral hypothalamic area (LHA) coordinates fundamental behavioral states such as sleep-wake patterns, feeding, metabolism, stress and motivated behavior. The wide spectrum of innate behaviors and physiological functions ascribed to the LHA may be explained by an exceptionally heterogeneous population of LHA cell types, the diversity of which is poorly understood. In this study, we implemented a single cell transcriptomic approach to classify molecularly distinct neuronal and non-neuronal cell types in the LHA. Specifically, we used a droplet-based single cell isolation method followed by RNA sequencing (scRNA-seq) of individual cells from the LHA, microdissected from juvenile male and female mice. Using unsupervised clustering and differential gene expression analysis to determine transcriptionally distinct cell types, we identified 11 non-neuronal cell types and 30 neuronal cell types. Neuronal cell types in the LHA could be parsed into 15 populations of glutamatergic (*Slc17a6*-expressing) and 15 populations of GABAergic (*Slc32a1*-expressing) neurons, each expressing a suite of discriminatory markers. Distinct neuronal populations were determined by a confluence of markers that includes neuropeptides, transcription factors, synaptic proteins, calcium-binding proteins among other gene categories. In addition to identifying novel cell populations in the LHA, we discovered the molecular basis for discriminating subpopulations of both known and novel cell types. Furthermore, we validated differentially expressed genes through fluorescence *in situ* hybridization (FISH) and single cell qPCR (sc-qPCR) profiling of a selection of genetically-labeled neuronal populations. This comprehensive, transcriptomic analysis of cell types in the LHA, at single cell resolution, lays the groundwork for understanding the molecular, cellular and circuit-level underpinnings of LHA orchestration of fundamental behavioral states, and their dysfunction in disease processes.

Disclosures: L.E. Mickelsen: None. **M. Bolisetty:** None. **B.R. Chimileski:** None. **A. Fujita:** None. **P. Robson:** None. **A.C. Jackson:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.18/WW3

Topic: F.10. Food Intake and Energy Balance

Support: BBRF 2015 Young Investigator NARSAD
Texas Woman's University Research Enhancement Program
Texas Woman's University Startup funds

Title: Hypothalamic MeCP2 protein levels are altered in mice exposed to high fat diet *in utero*

Authors: A. O'BRIEN[1], J. FRAYRE[2], M. J. MORRIS[1], *E. NA[1]
[1]Psychology & Philosophy, [2]Texas Woman's Univ., Denton, TX

Abstract: Obesity is a nationwide epidemic that affects approximately 30% of the adult population and also adversely affects children, with 1 in 3 children considered overweight. This alarming trend has been associated with cardiovascular disease, type 2 diabetes, as well as psychological disorders such as depression and anxiety. While genetics is a contributing factor, monogenic causes for obesity tend to be extremely rare particularly in childhood cases of obesity. We hypothesize that other biological factors such as epigenetic factors may contribute to the development of obesity in mice exposed to different gestational diets. Methyl-CpG-binding protein 2 (MeCP2) is one such epigenetic factor that is putatively involved in producing obesity in Prader-Willi syndrome children, a key symptom of which is hyperphagia. Here we examined the effects of gestational exposure to a high fat diet (HFD) in mice as compared to mice who were gestationally exposed to a diet that contained adequate levels of fat (NC: normal chow). We find that MeCP2 protein expression is elevated in the hypothalamus of mice exposed to HFD compared to mice exposed to NC during gestational development. MeCP2 protein levels are not altered in the hippocampus suggesting that exposure to HFD during gestation might be specific to areas of the brain that are responsive to changes in energy balance. We also show that body weight is substantially increased in mice that are maintained on HFD after weaning compared to mice that are maintained on NC diet. These data replicate past findings that exposure to HFD can produce obesity in mice. We also show that MeCP2 levels can be influenced by gestational diet and that perhaps MeCP2 may play a significant role in the etiology of obesity.

Disclosures: A. O'Brien: None. **J. Frayre:** None. **M.J. Morris:** None. **E. Na:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.19/WW4

Topic: F.04. Stress and the Brain

Support: KAKEN 16K10951, MEXT JAPAN
KAKEN 17K11066, MEXT JAPAN

Title: Nine candidate genes involved in postoperative nausea and vomiting: Transcriptome analysis in the nucleus of the solitary tract of the musk shrew

Authors: *D. KONNO[1], S. SUGINO[1], T. F. SHIBATA[2,3], K. MISAWA[2,3], Y. IMAMURA-KAWASAWA[4,5,6], K. KIDO[7], M. NAGASAKI[2,3], M. YAMAUCHI[1]
[1]Anesthesiol. and Perioperative Med., [2]Biomed. Information Analysis, Tohoku Univ. Grad. Sch. of Med., Sendai, Japan; [3]Integrative Genomics, Tohoku Univ. Tohoku Med. Megabank Organization, Sendai, Japan; [4]Genome Sci. and Bioinformatics Core, [5]Pharmacol., [6]Biochem. and Mol. Biol., Pennsylvania State Univ. Col. of Med., Hershey, PA; [7]Anesthesiol., Kanagawa Dent. Univ. Grad. Sch. of Dent., Yokosuka, Japan

Abstract: Background: Postoperative nausea and vomiting (PONV) is a serious complication after emergence from general anesthesia. However, the molecular mechanisms underlying PONV have not been fully elucidated. Musk shrews are used for emetic research worldwide because standard laboratory mammals, such as rats and mice, are not capable of vomiting. The aims of this study were to establish a shrew model of PONV and to determine changes in gene expression in the nucleus of the solitary tract, which is considered to be the vomiting center in the human brain. **Methods and Results:** Twenty-one female musk shrews (Jic:SUN-Her/Kwl strain, 7-10 weeks of age, weighing 30-50 g) were assigned to four groups and treated as follows: incision and suture of the lower abdomen under 5% of isoflurane inhalation (Surgery group, n = 9), 5% isoflurane inhalation alone (Sham group, n = 6), no treatment (Naïve group, n = 3), and nicotine administration alone as a positive control (PC group, n = 3). After the treatment, the shrews were transferred into an observation chamber to assess emesis for 30 minutes. Episodes of retching and/or vomiting when the interval between retches and/or vomits exceeded 2 seconds were counted. The numbers of episodes were 6 (8), 6 (1), 0 (0), and 12 (8) in the Surgery, Sham, Naïve, and PC groups, respectively [median (interquartile range), Kruskal-Wallis test, p = 0.066)]. After counting the episodes, each shrew was decapitated and the brain stem was immediately removed. The nucleus of the solitary tract was dissected from a frozen section of the brain stem, and total RNA was extracted from the nucleus. Whole transcriptome sequencing was then performed from three RNA samples in the Surgery group and three RNA samples in the Naïve group by using a next-generation DNA sequencer (Illumina HiSeq 2500). A total of 40 million paired-end reads (100 bp) were sequenced in each RNA sample. These reads were mapped to the shrew reference genome (Ous:KAT-227c strain, Suncus murinus Genome Project in Japan, unpublished draft sequence) by using Bowtie2 software. The mapped reads were assembled and annotated by using TIGAR software (Nariai et al., Bioinformatics 2013). Differential transcript expression levels were compared between two groups by using edgeR software. The expression levels of 52,381 transcripts were compared at a p value $< 10^{-5}$ and false discovery rate < 0.01. Nine genes, KIF1C, Ralgds, SDC3, MYRF, SNAP91, Itm2c, EHMT2, KCNIP4 and HSD17B12 genes, showed significantly different expression levels in two groups. **Conclusions:** We quantified changes in the whole transcriptome in the shrew nucleus of the solitary tract. Our results indicated that 9 genes may be involved in PONV.

Disclosures: S. Sugino: None. **T.F. Shibata:** None. **K. Misawa:** None. **Y. Imamura-Kawasawa:** None. **K. Kido:** None. **M. Nagasaki:** None. **M. Yamauchi:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.20/WW5

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817 to AMK
HHMI UTEP PERSIST Education Grant teaching assistantship to KN
NIH Grant 5G12MD007592 start-up funds to AMK
NIH Grant 1K01DK081937 to AMK
NIH Grant NS029728 to AGW
NIH Fellowship MH071108 to AMK
Keelung Hong Graduate Fellowship to EMW

Title: Hindbrain-originating catecholaminergic projections to the paraventricular hypothalamic nucleus are dispensable for recruitment of ERK1/2 in the lateral part of the central amygdalar nucleus following glycemic challenge in the rat

Authors: *A. M. KHAN[1], E. M. WALKER[1], K. NEGISHI[1], A. N. CLARK[1], A. G. WATTS[2]
[1]Dept. of Biol. Sci. and Border Biomed. Res. Ctr., Univ. of Texas at El Paso, El Paso, TX; [2]Biol. Sci., USC, Los Angeles, CA

Abstract: Hindbrain catecholaminergic (CA) neurons innervate and collateralize across many forebrain regions, including the arcuate (ARH) and paraventricular (PVH) hypothalamic nuclei and the central amygdalar nucleus (CEA). Using immunotoxin-based lesion methods, we have reported that certain PVH and ARH neurons require intact hindbrain-originating CA afferents in order to mount cellular responses to glycemic challenges (Khan et al., *J Neurosci*, 2011; *Endocrinol*, 2014). Here, we extend our long-term study of these same subjects (with either intact or lesioned CA afferents) by asking whether these projections to the PVH/ARH are also required for the lateral part of the CEA (CEAl) to respond to such challenges. To this end, we examined hindbrain CA afferents to the CEAl, as visualized by dopamine-β-hydroxylase-immunoreactive (DβH-ir); and CEAl neuronal activation 30 min after glycemic challenge, as visualized by elevations in phosphorylated ERK1/2 (pERK1/2)-ir neurons.
All intact (sham-lesioned) rats displayed modest DβH-ir fibers within the CEAl, in keeping with previous reports of the sparse but consistent presence of CA terminals in this amygdalar sub-region. The intact subgroup receiving i.v. saline displayed very few, if any, pERK1/2-ir neurons in the CEAl, whereas the subgroup receiving glycemic challenge (e.g., 2-deoxy-D-glucose; 250 mg/kg/ml, i.v.) displayed elevations of CEAl pERK1/2-ir neurons. Compared to intact rats, lesioned rats showing a loss of PVH/ARH DβH-ir fibers also displayed markedly reduced CEAl DβH-ir fibers. However, in contrast to what we reported for the PVH/ARH in these same

lesioned subjects, robust numbers of pERK1/2-ir neurons persisted in the CEAl of lesioned subjects. Our results show that phospho-ERK1/2 is recruited in CEAl neurons after glycemic challenge. Importantly, they also show that the CEAl contrasts with the PVH and ARH by its ability to mount robust cellular responses to glycemic challenge without intact hindbrain-originating CA afferents. Our findings suggest that another, as yet unidentified, ascending afferent system may relay these signals directly to the CEAl. The elevated numbers of neurons in the CEAl that display pERK1/2-ir could reflect activation of a descending, pre-autonomic component of a visceromotor system, a possibility well-supported by evidence that the CEAl helps to control autonomic function. These findings highlight the complex network interactions that occur across distributed sets of neuronal populations in the brain in association with a peripheral metabolic challenge.

Disclosures: A.M. Khan: None. **E.M. Walker:** None. **K. Negishi:** None. **A.N. Clark:** None. **A.G. Watts:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.21/WW6

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817 to AMK
HHMI UTEP PERSIST Education Grant teaching assistantship to BEP
NIH 8G12MD007592 (Border Biomedical Research Center)

Title: High-spatial resolution analysis of α-melanocyte stimulating hormone immunoreactivity in the adult male rat using a canonical brain atlas

Authors: *B. E. PINALES, A. M. KHAN
Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

Abstract: α-Melanocyte stimulating hormone (αMSH) has a prominent role in the regulation of energy expenditure. Despite research dedicated to understanding its anorexigenic effects, the precise distribution of αMSH-immunoreactive (ir) axonal fibers has yet to be delineated systematically. Here, we performed an immunocytochemical analysis of αMSH-ir chemoarchitecture in the rat forebrain and mapped the labeling patterns to a canonical rat brain atlas (L. W. Swanson, Brain Maps 4.0, 2018). Fixed coronal brain sections of an adult male Sprague-Dawley rat were incubated with a sheep polyclonal antibody (Millipore Cat# AB5087, RRID: AB_91683), and visualized with 3,3'-diaminobenzidine. Nissl-referenced cytoarchitecture and the use of camera lucida drawings allowed for the careful determination of plane of section. Data were mapped with the aid of a dark field microscope. A semi-quantitative

analysis of the labeled fiber distributions was undertaken with the use of Axiome C software (JD Hahn, SFN 2016, San Diego, #467.01. We found αMSH-ir fibers distributed within parts of the thalamus, amygdala, bed nuclei of the terminal stria (BST), and the hypothalamus. Areas of the highest density of αMSH-ir fibers include the lateral septum, medial preoptic nucleus, BST, paraventricular thalamic nucleus, paraventricular and periventricular hypothalamic nuclei, and the amygdala. Dense fibers were also seen in the dorsomedial and arcuate hypothalamic nuclei. Expression of moderate to sparse immunoreactive fibers was noted within the lateral hypothalamic area. αMSH-ir fibers were spread sparsely in the suprachiasmatic, anterior and ventromedial hypothalamic nuclei. Regions devoid of labeling included the cerebral cortex and certain subregions of the thalamus (including the anteromedial nucleus and ventral anterior lateral complex). In sum, we provide an initial series of high-spatial resolution digital atlas maps of αMSH distribution in portions of the rat forebrain. Together with our semi-quantitative analysis, these maps will help to streamline the precise targeting of experimental interventions in forebrain regions that receive αMSH innervation. Future analysis will extend to an examination of αMSH distribution in additional parts of the rostral forebrain.

Disclosures: B.E. Pinales: None. **A.M. Khan:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.22/WW7

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817 to AMK
NIH Grants RL5GM118969, TL4GM118971, and UL1GM118970 (BUILDing SCHOLARS Education Grants)

Title: Automatic derivation of atlas plate correspondences between rat brain atlases using feature-based matching and dynamic programming

Authors: *J. G. PEREZ[1], O. FUENTES[1], A. M. KHAN[2]
[1]Computer Sci., The Univ. of Texas at El Paso, El Paso, TX; [2]Dept. of Biol. Sci. and Border Biomed. Res. Ctr., Univ. of Texas at El Paso, El Paso, TX

Abstract: The rat brain is one of the most widely studied brains among all animals. Many experiments at multiple scales have been performed on it and numerous rat brain atlases have been published, several of which are now available online. However, correspondences between the several different atlases are not well defined. If these correspondences were available, neuroscientists who already mapped their data to one atlas could more easily translate their data to the other atlases. We developed an image-based algorithm that can automatically derive the

correspondences between all the plates of two different atlases. Our method works by first building a similarity matrix resulting from the comparison of the Nissl-stained tissue images of each plate from one atlas to the images in the other atlas using feature-based matching. These similarities are computed using the Scale Invariant Feature Transform (SIFT), allowing for a small degree of non-rigid transformation between images. Global correspondences between the atlases are then derived using the similarity matrix through a dynamic programming algorithm that enforces ordering constraints imposed by the atlas plate sequences. The dynamic programming algorithm is based on the traditional edit distance algorithm, with modifications made for usage on the domain of rat brain image matches instead of strings. We demonstrate the effectiveness of this algorithm by using it on the Swanson atlas (*Brain Maps, 3rd edition*, 2004) and the Paxinos & Watson atlas (*The Rat Brain in Stereotaxic Coordinates, 7th edition*, 2014) to derive correspondences between these two atlases. Four atlas levels that are fully in register between the two atlases by craniometric alignment were found to also match accurately using the dynamic programming algorithm, with an average accuracy to within one atlas level. These results show that this method is accurate and is comparable to correspondences derived by a neuroscientist through an image independent method; namely, that of craniometric alignments using stereotaxic coordinates. Through these correspondences, we provide a first step towards the development of a unified spatial model of the brain with registered and consistent datasets from diverse studies across multiple scales.

Disclosures: J.G. Perez: None. **O. Fuentes:** None. **A.M. Khan:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.23/WW8

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817 to AMK
HHMI UTEP PERSIST Education Grant teaching assistantship to KN
HHMI UTEP PERSIST Education Grant post-doc support to AM

Title: Hypothalamic chemoarchitecture of the adult male rat: High spatial resolution mapping of copeptin, LIM homeobox 6, and melanin-concentrating hormone

Authors: *A. MARTINEZ[1], L. M. BARRAZA ESCUDERO[1], D. CASTRO[1], S. A. CHAVEZ[1], M. CORONADO[1], S. GALLEGOS[1], A. PINEDA SANCHEZ[1], M. S. P. RUIZ[1], V. G. RUIZ[1], K. NEGISHI[1], A. M. KHAN[2]
[1]Biol. Sci., [2]Biol. Sci. and Border Biomed. Res. Ctr., Univ. of Texas at El Paso, El Paso, TX

Abstract: The hypothalamus is a key player in the control of homeostatic systems. While many complex networks involving hypothalamic peptides have been identified, their distributions remain poorly characterized. As a continuation of an ongoing hypothalamic mapping project undertaken annually by the HHMI-funded laboratory-based course (Brain Mapping & Connectomics), a team of undergraduate freshmen were taught how to conduct anatomical analyses of the hypothalamus in the adult male rat using Nissl-stained sections for cytoarchitectural analysis. To better understand the distributions of melanin concentrating hormone (MCH), copeptin, and LIM homeobox 6 (Lhx6), students combined immunofluorescence staining with formal atlas mapping techniques to digitally map the distributions of these molecules to the Swanson rat brain atlas (LW Swanson, Brain Maps 4.0, *J Comp Neurol*, 2018). MCH distribution was used as a reference dataset for direct comparisons between MCH maps generated by previous student cohorts to account for individual variability in mapping. Preliminary results of copeptin distribution in the hypothalamus corroborate previously reported data — it is present in the magnocellular populations of the hypothalamus (SO, PVHpml, NC) with extensive innervation of intra-hypothalamic structures. Further, our results show complementarity in the distributions of Lhx6 between the mouse and rat with labeling largely present in the anterior hypothalamus, absent at mid-lying levels and re-emerging at the level of the dorsomedial hypothalamus; specifically, in the dorsal and juxtadorsal lateral hypothalamic area and zona incerta. The maps from this effort represent the highest spatial resolution maps of copeptin and Lhx6 expression registered to a standardized rat brain atlas. These data continue to build upon our previous chemoarchitectural datasets to provide a better understanding of peptide distribution in the adult rat brain and a deeper understanding of hypothalamic circuitry.

Disclosures: A. Martinez: None. **L.M. Barraza Escudero:** None. **D. Castro:** None. **S.A. Chavez:** None. **M. Coronado:** None. **S. Gallegos:** None. **A. Pineda Sanchez:** None. **M.S.P. Ruiz:** None. **V.G. Ruiz:** None. **K. Negishi:** None. **A.M. Khan:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.24/WW9

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817 to AMK
HHMI UTEP PERSIST Education Grant

Title: High spatial resolution mapping of anorexigenic neuropeptides expressed in the hypothalamus: A chemoarchitecture study in the adult male rat

Authors: K. A. S. BURNETT[1], B. E. PINALES[1], E. J. PEREZ[1], D. RODARTE[1], A. M. CARDONA[1], K. J. GALVAN[1], G. G. HERNANDEZ[1], A. C. LEZAMA[1], K. T. LORENZANA[1], A. VASQUEZ[1], P. PARADA[1], J. I. PAZ[1], J. RASCON[1], R. THOMASON[1], K. BAUTISTA[1], J. BARNES[1], *C. D'ARCY[1], A. M. KHAN[2]
[1]Biol. Sci., Univ. Texas El Paso, El Paso, TX; [2]Dept. of Biol. Sci. and Border Biomed. Res. Ctr., Univ. of Texas at El Paso, El Paso, TX

Abstract: The hypothalamus is an important area for homeostatic regulation, due to its diverse population of chemical phenotypes. Although several studies have been dedicated to localizing these phenotypes, their overall spatial organization in relation to each other remains poorly understood. Here, we examine the distributions of neurons and axonal fibers immunoreactive for α-melanocyte stimulating hormone (αMSH) and cocaine- and amphetamine-regulated transcript (CART), both anorexigenic peptides, in relation to neurons and axonal fibers immunoreactive for tyrosine hydroxylase (TH) or neuronal nitric oxide synthase (nNOS). A cohort of freshman undergraduates was taught formal atlas mapping techniques within an HHMI-funded laboratory-based course. Multi-labeled immunofluorescent studies were performd on a male rat brain harvested under basal conditions. Fluorescently labeled immunostaining patterns were cross-mapped with a Nissl-stained tissue reference series to help localize chemoarchitectonic patterns in relation to the underlying cytoarchitecture. Plane of section analysis was carefully performed to facilitate the creation of high-spatial resolution digital maps of the chemoarchitecture within a canonical rat brain atlas (L. W. Swanson, *Brain Maps 4.0*, 2018). Patterns of 4,6-diaminidino-2-phenylindole (DAPI) labeling and immunostaining against the neuronal marker, NeuN, were also used for our analysis.The results show a widespread distribution of αMSH and CART immunoreactivities along the periventricular (pv) and paraventricular hypothalamic (PVH) nuclei, extending to sub-regions of the lateral hypothalamic area (LHA). There, these anorexigens partially colocalize within some areas. A few TH+ and nNOS+ cell bodies are expressed among their immunoreactive fiber distribution patterns, specifically along the margins of the periventricular hypothalamus (pv), where some neurons also appear to be sites of co-localization for both markers. TH+ cell bodies expressed along the pv also appear to be within the vicinity of both CART- and αMSH-immunoreactive fibers; further analysis will help to determine if these fibers form appositions with them. Ultimately, these data will provide high spatial resolution maps of peptides involved in feeding control. This effort will allow for precise functional targeting of specific chemical phenotypes and their comparison with other chemoarchitectural data mapped to the same canonical rat brain atlas (SFN 2015, Chicago, #616.08; SFN 2016, San Diego, #453.07; SFN 2017, Washington DC, #604.03).

Disclosures: K.A.S. Burnett: None. **B.E. Pinales:** None. **E.J. Perez:** None. **D. Rodarte:** None. **A.M. Cardona:** None. **K.J. Galvan:** None. **G.G. Hernandez:** None. **A.C. Lezama:** None. **K.T. Lorenzana:** None. **A. Vasquez:** None. **P. Parada:** None. **J.I. Paz:** None. **J. Rascon:** None. **R. Thomason:** None. **K. Bautista:** None. **J. Barnes:** None. **C. D'Arcy:** None. **A.M. Khan:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.25/WW10

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817 to AMK
HHMI UTEP PERSIST Education Grant teaching assistantship to KN
HHMI UTEP PERSIST Education Grant

Title: Spatial analysis of melanin-concentrating hormone axonal fiber distributions in the medial prefrontal cortex of the adult male rat

Authors: *E. MEJIA[1], A. ENRIQUEZ[2], K. NEGISHI[2], A. M. KHAN[3]
[1]1997, El Paso, TX; [2]Biol. Sci., [3]Dept. of Biol. Sci. and Border Biomed. Res. Ctr., Univ. of Texas at El Paso, El Paso, TX

Abstract: Melanin-concentrating hormone (MCH) is well-known for its contributions to motivated behaviors. An emerging view describes MCH as an integrative neuropeptide which modulates general arousal state in mammals. In support of this, MCH-containing axonal fibers reportedly distribute rather uniformly and with moderate densities within portions of the isocortex. However, these observations have not been examined thoroughly and there remains the possibility of subtle distinctions among cortical regions. Moreover, isocortex is known to contain a variety of GABAergic interneurons which are differentially involved in controlling behaviors. We used a cytoarchitecture-based approach to examine MCH-immunoreactive (-ir) axonal fiber distributions in the rat across coronal sections containing the medial prefrontal cortex (mPFC), beginning from the rostral end of the cortex to the genu of the corpus callosum. MCH-ir was present in low to moderate densities across all layers of the mPFC but a markedly denser innervation of layer 6 was observed in caudal parts of the infralimbic area and prelimbic cortex. Double label immunoperoxidase reactions were performed to visualize putative appositions between MCH and the prominent classes of interneurons - those that express either parvalbumin (PV) and somatostatin (SSt). Putative contacts were observed to a greater extent on SSt neurons than on PV neurons, despite PV neurons being more abundant. Interactions were more frequent in superficial layers of cortex than in deeper ones. A comparison between different areas of cortex showed that MCH-ir axons mainly targeted PV and SSt neurons in primary and secondary motor cortices. Interestingly, putative MCH-ir appositions were sparse in ventral mPFC areas despite the presence of MCH-ir axons. The maps from this effort could prove instrumental for targeting ultrastructural analyses needed to confirm the presence of synaptic interactions among these immunoreactive elements. Our findings also facilitate the design of functional investigations into bottom-up hypothalamic control of mPFC functions.

Disclosures: E. Mejia: None. **A. Enriquez:** None. **K. Negishi:** None. **A.M. Khan:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.26/WW11

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817 to AMK
HHMI UTEP PERSIST Education Grant teaching assistantship to KN
NIH 8G12MD007592 (Border Biomedical Research Center)

Title: Mesoscale characterization of medial prefrontal afferents from the hypothalamus: A spatial analysis of hypocretin/orexin and melanin-concentrating hormone neurons

Authors: *K. NEGISHI[1], A. M. KHAN[2]
[2]Dept. of Biol. Sci. and Border Biomed. Res. Ctr., [1]Univ. of Texas at El Paso, El Paso, TX

Abstract: Research on interactions between the prefrontal cortex and hypothalamus is typically focused on the top-down control of motivated behaviors. By comparison, less is known about the structural and functional underpinnings of bottom-up influences on cortical processes. Hypocretin/orexin (H/O) and melanin-concentrating hormone (MCH) are prominent among hypothalamic cell types. These neurons occupy overlapping fields concentrated in the caudal half of the lateral hypothalamic area (LHA). H/O and MCH are known to project throughout the CNS but it is unclear whether their cell bodies of origin are topographically organized or, conversely, if connections emerge stochastically. Furthermore, the proportions to which PFC-projecting LHA neurons express H/O and MCH is unclear. We begin to address these issues using injections of cholera toxin β subunit (CTB) into the medial prefrontal cortex (mPFC). We then used triple label immunohistochemistry to identify retrogradely labeled neurons which co-localized with MCH or H/O. An injection into the infralimbic area (ILA) produced labeling throughout the hypothalamus. Cell counts performed on coronal sections containing H/O and MCH revealed that 40.4% of retrogradely labeled neurons belonged to those groups. 28.8% of ILA-projecting neurons produced MCH (30/104) whereas 11.5% expressed H/O (12/104). An adjacent Nissl section was used to localize CTB-labeled cells. Most MCH-ir CTB neurons were concentrated in the ventromedial and dorsal (LHAd) parts of the LHA as well as the zona incerta (ZI) where, interestingly, all CTB-labeled cells expressed MCH. ILA-projecting H/O neurons were mainly found in the suprafornical region of the LHA and the posterior hypothalamic nucleus. In contrast to the ILA, an injection centered in the dorsal part of the anterior cingulate area produced sparse CTB labeling in MCH neurons of the LHAd and ZI. Collectively, these findings suggest that MCH and H/O populations could be further subdivided into projection-defined groups.

Disclosures: K. Negishi: None. **A.M. Khan:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.27/WW12

Topic: F.10. Food Intake and Energy Balance

Support: NSERC RGPIN-2017-06272 to MJC
NIH Grant GM109817 to AMK

Title: Identification and atlas mapping of mouse hypothalamic neurons that co-express tyrosine hydroxylase and the vesicular GABA transporter in *in situ* hybridization and immunohistochemistry studies

Authors: *M. J. CHEE[1], K. NEGISHI[2], K. SCHUMACKER[1], R. M. BUTLER[1], G. WITTMANN[4], A. M. KHAN[3]
[1]Carleton Univ., Ottawa, ON, Canada; [3]Dept. of Biol. Sci. and Border Biomed. Res. Ctr., [2]Univ. of Texas at El Paso, El Paso, TX; [4]Tufts Med. Sch., Boston, MA

Abstract: In order to study the chemoarchitecture of GABAergic neurons within the mouse hypothalamus, we examined GABAergic neurons that express the catecholamine-synthesizing enzyme, tyrosine hydroxylase (TH). We crossed the *Vgat-cre* mouse expressing Cre recombinase under the control of the vesicular GABA transporter (vGAT) promoter to a L10-EGFP reporter mouse to label the soma of vGAT neurons. To validate vGAT expression, we combined immunohistochemistry (IHC) and *in situ* hybridization (ISH) methodology to determine the presence of GFP-immunoreactivity (ir) in the vGAT-L10-EGFP hypothalamus. A careful examination of the combined IHC and ISH signals showed that nearly every EGFP-positive hypothalamic neuron expressed *Vgat* mRNA. We then performed dual-IHC against TH (mouse, 1:2000) and GFP (rabbit, 1:1000) on formalin-fixed vGAT-L10-EGFP brain tissue to map the distribution of TH/GFP. Furthermore, in order to contextualize the observed TH/GFP expression patterns, we used Nissl-stained datasets and nomenclature from the online Allen Brain Atlas (P56, coronal) to perform Nissl-based parcellation and plane-of-section analysis.
Several hypothalamic regions contained neurons that co-localized GFP+TH-ir. The zona incerta contained the most robust co-labeling of GFP+TH-ir neurons. Strikingly, this colocalization appeared specifically restricted to Level 67-68 of the Allen Brain Atlas. We also found a moderate density of GFP+TH-ir neurons within the anterior parvicellular part of the paraventricular hypothalamic nucleus (PVHap); the preoptic (PVpo) and intermediate (PVi) part of the periventricular hypothalamic nucleus; the anterior (DMHa), posterior (DMHp) and ventral (DMHv) part of the dorsomedial hypothalamic nucleus; and at various levels throughout the arcuate hypothalamic nucleus (ARH). Additionally, we found that GFP+TH-ir neurons do not

express dopamine beta-hydroxylase, suggesting that these neurons are not noradrenergic or adregnergic and hence are likely to be dopaminergic.
These results suggest the existence of a novel hypothalamic population that may signal through the release of GABA and/or dopamine. Further functional studies may confirm these structural findings and determine their physiological and behavioral roles.

Disclosures: M.J. Chee: None. **K. Negishi:** None. **K. Schumacker:** None. **R.M. Butler:** None. **G. Wittmann:** None. **A.M. Khan:** None.

Poster

680. Central Pathways Controlling Food Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 680.28/WW13

Topic: F.10. Food Intake and Energy Balance

Support: NIH OD010996
NIH NS099234

Title: Central circuitry involved in the control of brown and white adipose tissue in normal rats and obese rats fed with high energy diet from early age

Authors: *G. CANO[1], S. L. HERNAN[1], H. R. ALLEN[1], A. G. RICHIE[1], D. R. UKASIK[1], D. TUPONE[2], A. F. SVED[1]
[1]Univ. of Pittsburgh Dept. of Neurosci., Pittsburgh, PA; [2]Neurosurg., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Brown adipose tissue (BAT) regulates heat production to maintain body temperature, whereas white adipose tissue (WAT) functions as an energy reserve. Central control of BAT and WAT activity is exerted via direct sympathetic innervation. Obesity causes dramatic changes in BAT and WAT body distribution and reduces BAT thermogenic activity. We used a well-known model of diet-induced obesity (DIO) to examine whether early life obesity affects the central circuitry that controls BAT and WAT activity in rats. Preadolescent rats (28 days-old; n =24) were fed with high energy diet (31.8% kcal from fat; 25.2% kcal from sucrose) for 8 weeks, whereas control rats were fed with chow. The DIO model generates two subsets of rats based on body weight: obese (573.6 $\pm$ 17.1 g) and obese resistant (460.5 $\pm$ 14.1 g). Chow-fed rats were 491.4 $\pm$ 15.2 g. Each rat was injected with a strain of pseudorabies virus (PRV) that expresses RFP (PRV-614) into inguinal WAT and a PRV expressing GFP (PRV-152) into intrascapular BAT. Rats were perfused at different survival times (96-136 hours), and brains were removed and processed. At early survival times, WAT- and BAT-infected neurons were observed in brain regions involved in central sympathetic control. In chow-fed rats, dual-infected neurons were numerous in the rostroventrolateral medulla (RVLM) and the A5 group, whereas the raphe

pallidus (RPa) and the parapyramidal group (PPy) showed mostly BAT-infected neurons. In other regions such as the paraventricular hypothalamic nucleus (PVH) and ventral locus coeruleus (vLC), similar numbers of single and dual-infected neurons were intermixed. In obese rats, most infected neurons in RVLM and A5 were single-infected BAT neurons, whereas most dual-infected neurons were located in the gigantocellular formation. In RPa and PPy, single-infected BAT and WAT neurons were segregated. The PVH and vLC showed similar numbers of dual and single-infected neurons. At longer survival times, obese rats showed numerous dual infected neurons in regions involved in metabolic control such as the lateral hypothalamus (LH; Orexin-positive), arcuate nucleus (Arc) and Edinger-Westphal nucleus. Dual-infected neurons were also abundant in the preoptic area and the dorsomedial hypothalamic nucleus. Our results suggest that though the same brain regions control BAT and WAT in chow-fed and obese rats, there are some subtle differences in some brain regions (RVLM and A5). Brain areas with an important role in thermoregulation, such as the RPa and PPy, contain tissue-specific segregated neurons, whereas in brain regions involved in metabolic activity (LH and Arc) most neurons are connected to both WAT and BAT simultaneously.

Disclosures: G. Cano: None. **S.L. Hernan:** None. **H.R. Allen:** None. **A.G. Richie:** None. **D.R. Ukasik:** None. **D. Tupone:** None. **A.F. Sved:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.01/WW14

Topic: G.02. Motivation

Support: Collaborative Research Centre 1080

Title: Low nanomolar concentrations of isradipine selectively reduce *in vivo* burst firing of dopamine neurons in the lateral substantia nigra

Authors: *J. SHIN[1], L. KOVACHEVA[1], D. THOMAS[2], S. STOJANOVICH[1], C. A. PALADINI[3], G. GEISSLINGER[2], J. ROEPER[1]
[1]Inst. of Neurophysiology, Neurosci. Ctr., Frankfurt am Main, Germany; [2]Pharmazentrum frankfurt / ZAFES, Inst. of Clin. Pharmacol., Frankfurt am Main, Germany; [3]UTSA Neurosciences Inst., UTSA, San Antonio, TX

Abstract: Isradipine, a clinically approved L-type calcium channel inhibitor, is currently used in a clinical trial testing its ability to slow down the progression of Parkinson disease (PD-Steady III). Although there is evidence that isradipine reduces activity-dependent calcium loading of dopamine (DA) substantia nigra (SN) neurons in vitro, it is unknown whether isradipine affects the in vivo activity of DA SN neurons in therapeutically relevant concentrations. We have

previously presented evidence for a selective role of isradipine-sensitive L-type calcium channels in boosting in vitro burst excitability in lateral but not in medial DA SN neurons of adult C57Bl6N mice (Shin et al., SfN 2017). To now probe for a role of isradipine in the therapeutically relevant, low nanomolar concentration range in controlling in vivo bursting of DA SN neurons, we carried out single-unit recordings of DA SN neurons combined with juxtacellular labeling in anesthetized C57Bl6N mice. Systemic applications of 3 mg/kg isradipine (i.p.) resulted in a selective (ca. 40%) reduction of in vivo bursting of lateral DA SN neurons (spikes fired in bursts: control, 41.84 ± 26.48 %, isradipine, 25.69 ± 23.03 %, n=18, p=0.0006), while firing properties of medial DA SN neurons remained unaffected (spikes fired in bursts: control, 14.63 ± 18.67 %, isradipine, 14.65 ± 16.08 %, n=17, p=0.94). The maximal in vivo effect on bursting was observed at about 15 minutes after systemic drug application, which corresponded to a free plasma concentration of ca. 3 nM isradipine (22.53 ± 3.26 ng/ml at 15 min. post-injection, assuming 95% plasma protein binding, n=5). In vitro bath application of 3 nM isradipine was sufficient to induce a partial (ca. 35%) inhibition of burst excitability in lateral DA SN neurons (gain: control, 758.3 ± 120.3 Hz*nS, n=24, 300 nM isradipine, 425.9 ± 106.5 Hz*nS, n=17, 3 nM isradipine, 641 ± 181.8 Hz*nS, n=14) consistent with our in vivo results. We are currently probing for behavioral effects of low nanomolar isradipine locally infused into the lateral SN of freely moving mice to identify behavioral consequences of acutely suppressing burst activity in lateral SN DA neurons. In summary, our data identified a surprisingly selective in vivo effect of low nanomolar isradipine on burst firing of lateral SN DA neurons. These results constitute a new candidate mechanism how isradipine treatment might affect the most vulnerable DA subpopulation in Parkinson disease.

Disclosures: J. Shin: None. **L. Kovacheva:** None. **D. Thomas:** None. **S. Stojanovich:** None. **C.A. Paladini:** None. **G. Geisslinger:** None. **J. Roeper:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.02/XX1

Topic: G.02. Motivation

Support: Academy of Finland Grant
CIMO Grant
Finnish Pharmacological Society Travel Grant

Title: New players in reward ventral tegmental area circuitry in mice: Electrophysiological and anatomical characterization of somatostatin-positive neurons

Authors: *E. NAGAEVA[1], M. FORSS[1], I. ZUBAREV[2], L. ELSILÄ[1], E. DE MIGUEL[1], E. KORPI[1]

[1]Pharmacol., Univ. of Helsinki, Helsinki, Finland; [2]Dept. of Neurosci. and Biomed. Engin., Aalto Univ., Espoo, Finland

Abstract: The ventral tegmental area (VTA), a part of the midbrain, plays a crucial role in motivational and cognitive behaviors, natural rewards and the action of addictive drugs. All these behaviors require dopamine (DA) release from the VTA to other parts of the brain. Although the VTA serves as one of the main sources for DA neurons in the mammalian brain, it also contains about 25% inhibitory γ-aminobutyric acid-(GABA) and about 5% excitatory glutamate-releasing neurons.

Decoding of any neuronal circuitry requires detailed characterization of all its components. In last decade, anatomy and physiology of VTA dopamine neurons were extensively investigated, whereas much less is known about GABA neurons. Here, we took an attempt to describe heterogeneity of GABA neurons in mouse VTA.

First immunohistochemical experiments showed no parvalbumin neurons in VTA. Using somatostatin(Sst)-Cre mouse line, we were able to find positive neurons, which accounted around 7% of VTA cells population. Further whole-cell current-clamp recordings on Sst-neurons and objective clustering algorithm (principal component analysis + Gaussian mixture model) revealed 3 major electrophysiological subtypes: afterdepolarizing (ADP), high-frequency firing (HFF) and delayed neurons. These subtypes can be easily recognized not only by their firing patterns, but also by location within VTA. Thus, ADP neurons are the most abounded group (53%, N=335) and usually can be found in lateral part of VTA, preferably in parabrachial pigmented (PBP) nucleus. Although, HFF neurons repeat anatomical pattern of ADP neurons, amount of them is much less (19%). Delayed neurons (28%) are located exclusively in the medial-posterior part of VTA in parainterfascicular and paranigral nuclei (PIF, PN). All electrophysiological experiments were done on male/female mice with C57BL/6 background of age P17-P23. Anterograde tracing experiments of VTA Sst neurons showed long-range projections to lateral hypothalamus, central amygdala, paraventricular thalamic nucleus and bed nucleus of stria terminalis.

Overall, here we first time described VTA somatostatin neurons population. This allows including them as the players in the midbrain reward circuitry and form the basis for investigation of somatostatin role in this circuitry.

Disclosures: E. Nagaeva: None. **M. Forss:** None. **I. Zubarev:** None. **L. Elsilä:** None. **E. de Miguel:** None. **E. Korpi:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.03/XX2

Topic: G.02. Motivation

Support: Trinity University Murchison and Start-up funds

Title: Structural and functional changes of input-specific excitatory synapses on nigral dopamine cells caused by cocaine

Authors: K. WINDSOR[1], P. VOIT[1], A. TOLER[1], A. LITCH[1], S. HEMANI[1], A. KARLA[1], C. GUO[1], P. FERRER[1], *G. M. BEAUDOIN, III[2]
[2]Biol., [1]Trinity Univ., San Antonio, TX

Abstract: *In vivo* cocaine exposure has been shown to induce changes in excitatory synaptic responses to mesostriatal dopamine neurons. These neurons may be a part of the reward pathway and could be important for controlling motivation and addictive behavior. Previously, we have shown glutamatergic projections from the pedunculopontine tegmental nucleus (PPN) onto dopamine neurons in the substantia nigra pars compacta (SNc) have altered glutamatergic receptor ratios one day after a single injection of cocaine administered *in vivo*. We are now characterizing the underlying structural and functional changes at this synapse. Using optogenetics, we are able to label and activate PPN by injecting in mice a virus encoding a light operated cation channel called channelrhodopsin (ChR2) and yellow fluorescent protein (YFP). Thus, we have begun to characterize the postsynaptic responses of SNc dopamine neurons to excitatory projections from PPN to identify the receptor subunit composition at these glutamatergic subtypes. As expected, N-methyl-d-aspartate receptors (NMDARs), have a standard outward rectifying I-V relationship suggesting the presence of standard NMDAR1/2 heteromers. Additionally, distribution of NMDAR1 subunit localization is not globally affected by cocaine in SNc. We are using the YFP-labeled axons to identify changes in localization of glutamatergic subunits at these synapses on dopamine neurons. We have developed an automated image analysis routine to identify putative synapses between PPN and dopamine neurons from confocal images in order to assay changes in localization of specific glutamate receptor subunits. By measuring the synaptic response of dopamine neurons and imaging the synapse, we have been able to begin characterizing what is affected by cocaine at these synapses.

Disclosures: K. Windsor: None. **P. Voit:** None. **A. Toler:** None. **A. Litch:** None. **S. Hemani:** None. **A. Karla:** None. **C. Guo:** None. **P. Ferrer:** None. **G.M. Beaudoin:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.04/XX3

Topic: G.02. Motivation

Support: F31DA041303
MH079276

GM060655

Title: Glutamate transporters on ventral tegmental area astrocytes orchestrate avoidance and approach behaviors

Authors: *J. A. GOMEZ[1], J. PERKINS[2], G. M. BEAUDOIN, III[3], N. COOK[1], S. QURAISHI[1], M. J. WANAT[4], C. A. PALADINI[5]
[2]Biol., [1]The Univ. of Texas at San Antonio, San Antonio, TX; [3]Biol., Trinity Univ., San Antonio, TX; [4]Neurosciences Inst., Univ. of Texas at San Antonio, San Antonio, TX; [5]UTSA Neurosciences Inst., UTSA, San Antonio, TX

Abstract: Approach and avoidance responses are critical behaviors for survival that signify adaptive responses toward rewarding cues and away from aversive cues, respectively. The ventral tegmental area (VTA) is a heterogeneous midbrain structure that integrates distributed signals for both rewarding and aversive cues, but mechanistic studies have focused exclusively on manipulations of neurons. Whether astrocytes influence local VTA circuit signaling to effect motivated behavior remains unexplored. Here we demonstrate that VTA astrocytes control approach and avoidance behavior by mediating glutamatergic excitation of local GABA neurons. Loss of the glutamate transporter, GLT-1, from VTA astrocytes reduced approach-avoidance conflict in favor of approach. We found that astrocytic GLT-1 in the VTA mediated an increase in excitation of local GABA neurons that elicited a subsequent increase in inhibition of VTA dopamine neurons. The GLT-1-mediated excitation of local GABA neurons resulted in learned avoidance of cues associated with aversion, and prevented expression of preference for cues associated with reward. These data establish an endogenous VTA mechanism wherein astrocyte GLT-1 kinetics control GABAergic tone in the local circuit to shift expression between approach and avoidance behavior. This work suggests VTA astrocytes may be a compelling substrate for studying maladaptive failures of avoidance.

Disclosures: J.A. Gomez: None. **J. Perkins:** None. **G.M. Beaudoin:** None. **N. Cook:** None. **S. Quraishi:** None. **M.J. Wanat:** None. **C.A. Paladini:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.05/XX4

Topic: G.02. Motivation

Support: CIHR, MOP-81321
CIHR MOP-130407
NSERC RGPIN-2015-05018

Title: GluN2C-containing NMDA receptors relay the reward signal in the ventral tegmental area

Authors: *G. A. HERNANDEZ[1], E. POIRIER[2], W. M. KOUWENHOVEN[2], D. LÉVESQUE[2], P.-P. ROMPRÉ[2]
[1]Physiologie, [2]Neurosci., Univ. de Montreal, Montreal, QC, Canada

Abstract: Studies on how the reward signal is transmitted in the brain had identified glutamate neurotransmission as an important component in the reward circuitry. Glutamate (Glu) relays the reward signal from the dorsal raphe to ventral tegmental area (VTA) dopamine (DA) neurons. It controls the switch from tonic to phasic firing in active DA neurons, the latter being associated with reward signaling. Also, Glu plays a role in the maintenance of DA inhibitory drive. This myriad of roles suggests that different Glu receptors are involved in these different functions. Here we studied the effects of VTA down-regulation of GluN2C-containing NMDA receptor on the reward signal that arises from dorsal raphe (DR) electrical stimulation. After rats were implanted with an electrode aimed at the DR and bilateral cannulae aimed at the VTA, they were trained to self-stimulate, and reward thresholds were measured using the curve-shift paradigm. Once stable behavioral measurements were obtained, small interfering RNA (siRNA) against GluN2C subunit or a non-active RNA sequence was microinjected into the VTA (5 µg per side); 24 h after each of the 2 consecutive daily bilateral VTA microinjections, reward thresholds were obtained. After the last measurement, reward thresholds were reassessed once rats received a bilateral VTA microinjection (0.825 nmol/0.5 µl/side) of the NMDA receptor antagonist, PPPA. Brains were harvested, and tissue punches from the VTA were taken to determine via Western-blot the levels of specific NMDA receptor subunits (GluN2C and GluN2A). The siRNA treatment produced a selective down-regulation of the GluN2C subunit (~40%) and a significant reduction in reward pursuit. Interestingly, the NMDA antagonist PPPA enhanced reward pursuit only in those rats that received the non-active RNA sequence. Thus, the present results suggest that VTA Glu neurotransmission relays the reward signal initiated by DR electrical stimulation by acting on GluN2C-containing NMDA receptors.

Disclosures: G.A. Hernandez: None. **E. Poirier:** None. **W.M. Kouwenhoven:** None. **D. Lévesque:** None. **P. Rompré:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.06/XX5

Topic: G.02. Motivation

Support: NIH Grant MH113341

Title: *In vivo* characterization of dopamine neuron subthreshold activity

Authors: *J. M. PERKINS[1], A. S. KULKARNI[1], K. M. COSTA[2], J. ROEPER[3], C. A. PALADINI[4]
[1]Univ. of Texas at San Antonio, San Antonio, TX; [2]Inst. for Neurophysiol., Goethe Univ., Frankfurt am Main, Germany; [3]Goethe Univ. Frankfurt, Frankfurt, Germany; [4]UTSA Neurosciences Inst., UTSA, San Antonio, TX

Abstract: Changes in dopamine neuron firing activity are the result of dynamic changes in synaptic input. Previous extracellular in vivo studies have not been able to measure subthreshold ionic conductances driven by constant activity from both excitatory and inhibitory afferents. Intracellular in vivo recording is the ideal method for measuring changes in firing activity resulting from changes in subthreshold ionic conductances. We have developed a method to consistently obtain in vivo whole-cell recordings from dopamine neurons. Using intracellular in vivo recordings, we are able to differentiate the excitatory and inhibitory subthreshold ionic conductances that elicit either an increase or decrease in dopamine firing activity. We found that the majority of ventral midbrain dopamine neurons have a larger proportion of inhibitory conductance than excitatory conductance.

Disclosures: J.M. Perkins: None. **A.S. Kulkarni:** None. **K.M. Costa:** None. **J. Roeper:** None. **C.A. Paladini:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.07/XX6

Topic: G.02. Motivation

Support: NIH Grant MH079276

Title: Glt-1 on astrocytes in the vta regulates cocaine-seeking behavior

Authors: *N. COOK[1], A. S. KULKARNI[3], J. A. GOMEZ[4], C. A. PALADINI[2]
[1]Neurosciences Inst., [2]UTSA Neurosciences Inst., UTSA, San Antonio, TX; [3]Univ. of Texas At San Antonio, San Antonio, TX; [4]The Univ. of Texas At San Antonio, San Antonio, TX

Abstract: The ventral tegmental area (VTA) plays an important, yet complex role in processing a reward (e.g. cocaine). It is known that GLT-1 on astrocytes is mainly involved in regulating extracellular glutamate concentrations surrounding neurons. However, it is unknown if the level of GLT-1 expression in VTA astrocytes affects cocaine-seeking behavior. Here, we examine a connection between GLT-1 levels in mice and their infusion rates during self-administration of cocaine. First, in control mice, we show there are variable levels of self-administration. We will measure the correlation between infusion rates and GLT-1 expression. Second, to show the

impact of astrocytic GLT-1 in the VTA on behavior we used a GLT-1 conditional knock out (cKO) specific to astrocytes in the VTA. Our results demonstrate a decrease in the expression of GLT-1 levels in the VTA can alter cocaine-seeking behavior in mice. GLT-1 cKO mice demonstrate low infusion rates when self administering cocaine. Our results indicate GLT-1 on astrocytes regulate cocaine-seeking behavior in the VTA.

Disclosures: N. Cook: None. **A.S. Kulkarni:** None. **J.A. Gomez:** None. **C.A. Paladini:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.08/XX7

Topic: G.02. Motivation

Support: The Obesity Society Postdoctoral Fellowship

Title: Hypothalamic - habenular - midbrain communication differentially regulates food preference in lean and obese rodents

Authors: *R. M. O'CONNOR, M. V. M. DI BONAVENTURA, W. M. HOWE, A. G. DIFELICEANTONIO, K. DEVARAKONDA, P. J. KENNY
Icahn Sch. of Medicine, Mount Sinai, New York, NY

Abstract: Rates of obesity are on the rise worldwide, resulting in a growing threat to public health. Pharmacotherapies that safely reduce body weight in obesity remain elusive, partially due to our incomplete knowledge of the complex neuronal mechanisms that control food choice (palatable high-calorie versus less palatable low-calorie food). The lateral hypothalamus (LH) is considered a critical node in the maintenance of energy homeostasis. A major output of the LH terminates in the lateral habenula (LHb) which has been described as a “preference center” and exerts a negative influence over motivated behaviors through inhibition of midbrain dopamine neurons. We tested the hypothesis that LH projections to LHb play an important role in food preference and food-related motivation through downstream influences on midbrain dopamine neurons. Using monosynaptic rabies tracing we found prominent innervation of ventral tegmental area (VTA) projecting LHb neurons originating in LH. Using fiber photometry, we found neuronal activity of these VTA projecting LHb neurons decreased in hungry animals during the retrieval of regular rodent chow rewards (homeostatic feeding) and in sated animals during palatable food consumption (hedonic feeding). In lean animals the magnitude of decreased neuronal firing from baseline was greatest for homeostatic food seeking compared to hedonic. Interestingly, this pattern switched when animals became obese through exposure to a cafeteria style diet and hedonic seeking of highly palatable food now dramatically reduced VTA projecting LHb neuronal activity. DREADD-mediated stimulation of the LH inputs to the LHb

decreased consumption of palatable energy-dense food, whereas ablation of this pathway increases consumption of the palatable food; opposite effects of these manipulations were observed when only standard (less palatable) chow was made available. Based on these findings, we hypothesize that deficits in the LH - LHb - VTA circuit may emerge during weight gain and contribute to obesity-associated behavioral abnormalities. Modulation of activity at this circuit may represent a promising therapeutic strategy for reversing hyperphagic feeding patterns that generate and maintain obesity.

Disclosures: R.M. O'Connor: None. **M.V.M. Di Bonaventura:** None. **W.M. Howe:** None. **A.G. DiFeliceantonio:** None. **K. Devarakonda:** None. **P.J. Kenny:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.09/XX8

Topic: G.02. Motivation

Support: DA038453
NS098615

Title: β-arrestin2 in dopamine receptor-containing neurons modulates the behavioral effects of cocaine and morphine

Authors: *K. A. PORTER-STRANSKY[1], S. L. KARNE[1], C. JEROME[1], N. M. URS[2], M. G. CARON[3], D. WEINSHENKER[4]
[1]Emory Univ., Atlanta, GA; [2]Dept. of Pharmacol. and Therapeut., Univ. of Florida, Gainesville, FL; [3]Duke Univ. Hosp., Durham, NC; [4]Dept Human Genet., Emory Univ. Sch. Med., Atlanta, GA

Abstract: Psychostimulants and opioids increase dopamine release, thereby promoting neurotransmission through dopamine receptors. The protein β-arrestin2 (βarr2) is important for desensitizing and internalizing G protein-coupled receptors (GPCRs), including dopamine receptors, and can also initiate G protein-independent signaling cascades following GPCR activation. Previous work has shown that mice lacking βarr2 globally have altered responses to drugs of abuse, but the specific neurons and circuits mediating these effects are unknown. By crossing D1-Cre and D2-Cre transgenic mice with floxed βarr2 mice, we generated mice that lack βarr2 only in neurons containing either D1 ($D1^{\beta arr2\text{-}KO}$) or D2 ($D2^{\beta arr2\text{-}KO}$) dopamine receptors and then examined drug-induced locomotion and reward (using conditioned place preference; CPP) following multiple doses of D1- and D2-like agonists, cocaine, and morphine. While $D1^{\beta arr2\text{-}KO}$ mice had normal drug responses, $D2^{\beta arr2\text{-}KO}$ mice showed dose-dependent reductions in locomotor responses to cocaine, morphine, and the D2 receptor agonist quinpirole,

as well as a blunted CPP for cocaine. Interestingly, both $D2^{\beta arr2\text{-}KO}$ and $D1^{\beta arr2\text{-}KO}$ mice displayed an enhanced CPP for morphine. These results indicate that βarr2 is necessary in D2 neurons for the rewarding and locomotor-activating effects of psychostimulants, while both D1 and D2 neuron-derived βarr2 can modulate the rewarding effects of morphine.

Disclosures: K.A. Porter-Stransky: None. **S.L. Karne:** None. **C. Jerome:** None. **N.M. Urs:** None. **M.G. Caron:** None. **D. Weinshenker:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.10/XX9

Topic: G.02. Motivation

Support: NIH Grant DA038453

Title: Deletion of β-arrestin2 in D2-expressing cells alters dopamine, but not morphine sensitivity in D2 nucleus accumbens neurons

Authors: *A. K. PETKO[1], C. JEROME[2], M. G. CARON[3], N. URS[4], D. WEINSHENKER[2], C. PALADINI, 78249[1]
[1]Univ. of Texas at San Antonio, San Antonio, TX; [2]Dept Human Genet., Emory Univ. Sch. Med., Atlanta, GA; [3]Duke Univ. Hosp., Durham, NC; [4]Cell Biol., Duke Univ., Durham, NC

Abstract: G-protein coupled receptors such as opioid and dopamine receptors are coupled to β-arrestin2 (βarr2), which is an important regulator of receptor function. Within the nucleus accumbens (NAc), D1, D2 and μ-opioid receptors expressed on medium spiny neurons (MSNs) are subject to modulation by βarr2. Global deletion of βarr2 alters behavioral sensitivity to drugs of abuse, such as cocaine and morphine, but the cellular subtype and underlying mechanisms responsible are not known. Here, we examined psychostimulant and opiate responses in mice with a conditional βarr2 knockout in either D1 or D2 cells. Using slice electrophysiology, we found that the dopamine-mediated decrease in firing rate of D2 NAc MSNs observed in wild-type mice was attenuated in D2 βarr2 knockout animals, while the typical dopamine-induced increase in firing rate of D1 NAc MSNs was preserved in the mutants. Furthermore, we have found that morphine application similarly decreases maximum firing rate in D1 and D2 MSNs in βarr2 KO and control animals, suggesting that the change in sensitivity to morphine in βarr2 KO mice are likely a component of the dopamine-dependent pathway. Combined, our findings demonstrate a unique role for βarr2 in D2 NAc MSNs.

Disclosures: A.K. Petko: None. **C. Jerome:** None. **M.G. Caron:** None. **N. Urs:** None. **D. Weinshenker:** None. **C. Paladini:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.11/XX10

Topic: G.02. Motivation

Support: Department of Neuroscience Start-up Funds
NIH Grant R00DC013555

Title: Neuronal cilia mediate neuromodulatory signaling in a food-motivated progressive ratio task

Authors: *J. MCINTYRE[1], K. R. JASSO[1], V. CAMPANO[1], B. LEWIS[1], S. PARKS[1], B. SETLOW[2]
[1]Neurosci., [2]Psychiatry, Univ. of Florida, Gainesville, FL

Abstract: The neural mechanisms that underlie motivated behaviors and substance use disorders are complex, and impacted by numerous factors. These additional factors include several neuromodulatory peptides associated with physiological states such as hunger and satiety. Several of the receptors for these neuromodulators are enriched in the primary cilia of neurons. Primary cilia are microtubule-based organelles that project from the surface of nearly all mammalian cells, including neurons. The importance of cilia function in human health is highlighted by the number of diseases that result from primary cilia dysfunction, many associated with cognitive and behavioral abnormalities. Despite what we know about cilia, our understanding of how cilia regulate neuronal function and behavior is still limited. One potential mechanism is to provide a signaling platform for neuromodulatory peptides. Several g-protein coupled receptors (GPCRs), such as melanin-concentrating hormone receptor 1 (MCHR1), are enriched in the membrane of cilia compared to the cell body. MCH is a known modulator of feeding behavior, and also modulates behavioral responses to drugs of abuse. The primary objective of this study was to investigate the role of primary cilia in regulating the behavioral effects of MCH on food-motivated behaviors. Using genetic approaches, we selectively ablated cilia from dopaminergic or GABAergic neurons in mice. We then tested whether cilia loss on either of these neuron populations alters motivational state using a food-rewarded progressive ratio task. To assess the role of cilia in MCH signaling in this task, mice were tested following systemic injection of the MCHR1 antagonist SNAP-94847. Compared to wildtypes, mice lacking cilia on GABAergic neurons showed a significant reduction in progressive ratio breakpoint (i.e., reduced food motivation), whereas mice lacking cilia on dopaminergic neurons were unaffected. SNAP-94847 dose-dependently reduced breakpoint in both wildtype mice and mice lacking cilia on dopaminergic neurons, providing further evidence for MCH effects on motivated behavior and indicating that MCHR1 signaling on dopaminergic neuronal cilia is not critical for

modulating food-seeking. In contrast, SNAP-94847 had no effect on breakpoint in mice lacking cilia on GABAergic neurons. These results provide evidence that cilia on GABAergic neurons are important for regulating motivated behavior, and are necessary for MCHR1 modulation of food-seeking behavior. Future work will investigate the neuroanatomical locus of these effects, as well as the role of ciliary neuromodulation in responses to drugs of abuse.

Disclosures: J. McIntyre: None. **K.R. Jasso:** None. **V. Campano:** None. **B. Lewis:** None. **S. Parks:** None. **B. Setlow:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.12/XX11

Topic: G.02. Motivation

Support: CONACYT 261420
CONACYT 255317

Title: Nutritional programming during pregnancy and lactation sensitizes food addiction-like behavior in offspring of rats

Authors: *L. MONTALVO MARTINEZ[1], L. A. REYES-CASTRO[2], E. ZAMBRANO-GONZALEZ[2], R. ORTIZ-LÓPEZ, 64250[3], A. CAMACHO[4]
[1]Autonomous Univ. of Nuevo León, Ciudad Santa Catarina, Mexico; [2]Reproduction Biol., Natl. Inst. of Med. Sci. and Nutr. Salvador Zubirán, Tlalpan, Mexico; [3]Sch. of Med. and Hlth. Sci., Technological Inst. and of Superior Studies of Monterrey, MONTERREY, Mexico; [4]Univ. Autónoma de Nuevo León, Nuevo León, Mexico

Abstract: Obesity associates to excessive hypercaloric food intake leading to increase in body mass index. Incentive motivation to hypercaloric foods is partly related to an addictive-like behavior phenotype. Addiction correlates with selective changes in gene expression in specific brain reward regions, including the Nucleus Accumbens (NAc), which might be potentially transmitted to the offspring by transgenerational inheritance. Here, we used a murine model of maternal nutritional programming to determine whether: 1) addiction-like behavior of mothers is transmitted to male offspring (F1), and 2) candidate genes for food addiction in the NAc of addicted F1 correlates to aberrant synaptic plasticity gene profile found in drug addiction. We used 9 groups of Wistar rats (8-10 weeks of age), including 2 groups of females (F0) exposed for 9 weeks (pre-mating, pregnancy and lactation) to hypercaloric diet (HD) (maternal programming) or control diet (CD) (control group). All groups were trained by operant conditioning protocols (FR1, FR5, PR; 12 days) using a Skinner-type box, following by chocolate pellets as a reward to determine its addiction-like behavior. Microarray analysis from

the NAcshell of the offspring was performed to identify candidate genes. Our results show no changes in addiction-like behavior of F0 males and F0 females fed with CD. By contrast, F0 females fed with CD show enhanced motivation to hypercaloric rewards compared to F0 females fed HD. Of note, addiction-like behavior from F0 females fed HD was efficiently transmitted to the F1 male offspring in compare to F0 females fed CD. Likewise, global expression microarrays analysis showed that addiction-like
behavior subjects exhibit alteration in the expression of several genes involved in drug addiction such as: DR2, GluA1, GluA2, GluA3, BDNF, CREB, FosB, SIRT1, HDAC1, HDAC4 and MEF2. Genomic interaction pathways demonstrated interactive nodes involved in synaptic plasticity and neuronal function. Our results demonstrate that maternal hypercaloric programming sets food addiction-like behavior susceptibility which positively is transmitted to F1 male offspring showing selective gene expression changes in NAc shares during drug addiction phenotype.

Disclosures: L. Montalvo Martinez: None. **L.A. Reyes-Castro:** None. **E. Zambrano-Gonzalez:** None. **R. Ortiz-López:** None. **A. Camacho:** None.

Poster

681. Reward and Cell Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 681.13/XX12

Topic: G.02. Motivation

Title: Reward and punishment encodingencoding has shown divisive normalization in primary motor cortex

Authors: *Y. ZHAO[1], J. P. HESSBURG[2], J. T. FRANCIS[3]
[1]Biomed. Engin., [2]Physiol. and Pharmacol., [3]SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: Neural activity in the primary motor cortex (M1) is known to correlate with movement related variables including kinematics and dynamics. Recent studies have shown that M1 units are also modulated by reward signals. Divisive normalization encoding has been seen in many neural systems, like invertebrate olfactory system, retina and primary visual cortex. In this study, we investigated the reward and punishment modulation in M1 using divisive normalization model. Two non-human primates (NHPs), which were implant M1, have done the cued grip force task manually with different reward and punishment levels. The results have shown that M1 units, which modulated kinematics information, can have either motivation or valence modulation. These two modulation can be explained using the same divisive normalization model. Motivation units have shown linear or sigmoid relationship with stimuli (reward and punishment). Valence units have shown hyperbola relationship with stimuli and can be interpreted as “pleasant” or “willingness” encoding. Both motivation and valence units have

shown that they are sensitive for some particular reward and punishment levels, like receptor fields in primary visual cortex. These findings support the circumplex model of affect and provide new understanding on decision making process and emotion encoding.

Disclosures: Y. Zhao: None. **J.P. Hessburg:** None. **J.T. Francis:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.01/XX13

Topic: G.06. Post-traumatic Stress Disorder

Support: GVSU Catalyst Grant, CSCE
GVSU McNair
GVSU Psychology Department
GVSU Early Faculty Supplemental Startup, CSCE

Title: "Unhealthy" diet high in fat or sucrose on negative valence behavior in mice

Authors: *E. I. FLANDREAU[1], D. EUDAVE[1], M. BELOW[1], A. BUCHHEIT[2]
[1]Psychology, [2]Grand Valley State Univ., Allendale, MI

Abstract: Stress increases risk for psychopathology, but most stress-exposed individuals do not develop deleterious effects; other genetic and environmental factors moderate the risk for stress-induced psychopathology. A “Western” diet has been linked to psychopathology in humans; animal studies also show that diet can influence negative valence behavior in the presence or absence of stress, but findings are inconsistent, highlighting the need for additional research. The present study exposed mice to 10 days of high fat or high sucrose diet concurrent with social defeat stress and examined behavior in the social interaction, open field, elevated zero, tail suspension, and acoustic startle tests at acute (less than five days) and long-term (more than 30 days) time points after stress/diet exposure. In contrast to our hypothesis, we primarily observed main effects of stress or diet rather than stress x diet interactions. Stress increased negative valence behavior in these tests at the acute time point. Most stress-induced behaviors normalized after a 30-day recovery period, but social avoidance was still highly significant for stress-exposed mice, supporting the hypothesis that avoidance of trauma-related cues persists beyond non-specific anxiety-like behaviors. Supporting the hypothesis that an unhealthy diet contributes to psychopathology, non-stressed mice fed high fat or high sucrose diets spent less time exploring the center of the open field.

Disclosures: E.I. Flandreau: None. **D. Eudave:** None. **M. BeLow:** None. **A. Buchheit:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.02/XX14

Topic: G.06. Post-traumatic Stress Disorder

Title: Chemogenetic activation of medial prefrontal cortex excitatory neurons alleviated the impaired fear extinction of an animal model of PTSD

Authors: *J. OMURA[1], M. FUCHIKAMI[1], M. ARAKI[1], T. MIYAGI[1], S. MORINOBU[2]
[1]Psychiatry and Neurosciences, Hiroshima Univ., Hiroshima-Shi, Japan; [2]Kibi Intl. Univ., Okayama, Japan

Abstract: Although the impaired *extinction of fear memory* (EFM) is one of the hallmark symptoms of posttraumatic stress disorder (PTSD), the precise mechanisms of impaired EFM are unknown and effective pharmacological interventions have not yet been developed. A growing evidence shows that the activation of infralimbic cortex (IL), subregion of the medial prefrontal cortex (mPFC), predicts successful fear extinction, whereas functionally disrupting this region impairs extinction. We used a single prolonged stress (SPS) paradigm, which mimics the pathophysiological abnormalities and behavioral characteristics of PTSD including the impaired EFM. This study was undertaken to examine whether chemogenetic activation (CA) of mPFC excitatory neurons alleviated the impaired EFM in SPS. The CA was conducted by administration of clozapine-N-oxide (CNO) to activate virally delivered CamKII alpha-hM3Dq-DREADD in mPFC excitatory neurons, and the behavioral effect was examined using contextual fear conditioning. In addition, the effects of CA on the neuronal activity in sham and SPS rats were measured by multi-unit extracellular recording. The CA of IL, but not PL, just before extinction training significantly decreased freezing during the extinction training and extinction test (24h after extinction training) in sham rats, whereas this enhancement of EFM was only seen during the extinction test in SPS rats. Electrophysiological study revealed that the induction of neuronal activation by CA in IL of SPS rats was smaller than that of sham rats, though basal activity (without CA) in SPS rats was almost equal to that in sham. Our results indicates that the decreased excitatory tone in IL might, at least in part, be involved in the mechanism of the impaired EFM in SPS, and the simultaneous treatment with neuronal activation and exposure therapy may be effective in the treatment of patients with PTSD.

Disclosures: J. Omura: None. **M. Fuchikami:** None. **M. Araki:** None. **T. Miyagi:** None. **S. Morinobu:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.03/YY1

Topic: G.06. Post-traumatic Stress Disorder

Support: KAKENHI 16k21532

Title: Effects of intracerebroventricular administration of CGRP on fear response

Authors: *S. MISHIMA[1], A. OTSUKA[2], K. FUKUMOCHI[2], K. NISHIMURA[2], N. HASHIKAWA[2], N. HASHIKAWA-HOBARA[3]
[1]Okayama Univercity of Sci., Okayama-shi, Japan; [3]Life Sci., [2]Okayama Univ. of Sci., Okayama, Japan

Abstract: Calcitonin gene-related peptide (CGRP), which is produced in both peripheral and central nervous system, is well known as a potent vasodilator. Although CGRP plays an important role in central nervous system, its effect on hippocampus-dependent fear memory is still not clear. 8-week-old male C57BL6J mice were examined to passive avoidance test or contextual fear learning test. Mice were given a 0.2 mA foot shock when entered black compartment. In the contextual fear learning test, mice were given a 0.3 mA foot shock. After fear conditioning, mice were given saline or CGRP (0.5 nmol) by intracerebroventricular administration. CGRP injections shortened the avoidance latency in passive avoidance test, and also reduced freezing time in contextual fear learning test. To examine which gene is involved in CGRP-mediated extinction of fear memory, microarray assay was performed. CGRP injections significantly increased *Npas4* gene rather than saline treatment. We also found that CGRP increased dephosphorylation of nuclear histone deacetylase 5 (HDAC5), which is known to be involved in epigenetic regulation of NPAS4, in the mouse hippocampus. These results suggest that HDAC5 and NPAS4 might be involved in CGRP-mediated extinction of fear memory.

Disclosures: S. Mishima: None. **A. Otsuka:** None. **K. Fukumochi:** None. **K. Nishimura:** None. **N. Hashikawa:** None. **N. Hashikawa-Hobara:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.04/YY2

Topic: G.06. Post-traumatic Stress Disorder

Title: The role of glucocorticoid receptor in the induction and the prevention of the hippocampal abnormalities in an animal model of PTSD

Authors: *M. ARAKI[1], M. FUCHIKAMI[1], J. OMURA[1], T. MIYAGI[1], S. MORINOBU[2]
[1]Psychiatry and Neurosciences, Hiroshima Univ., Hiroshima-Shi, Japan; [2]Kibi Intl. Univ., Okayama, Japan

Abstract: Posttraumatic stress disorder (PTSD) is a representative stress-related mental disorder associated with an intricate biological and psychological symptom profile. Although the detailed mechanisms are not fully uncovered, numerous clinical studies of PTSD demonstrates the functional and morphological abnormalities in the hippocampus after exposure to life-threatening trauma, such as the enhanced negative feedback of the hypothalamo-pituitary-adrenal axis, hippocampal atrophy, and fear memory extinction. In this context, it is worthwhile to examine the alteration of hippocampal gene expression through glucocorticoid receptor (GR) in an animal model of PTSD to elucidate the pathophysiology of PTSD.
We used a single prolonged stress (SPS) paradigm, which mimic the pathophysiological abnormalities and behavioral characteristics of PTSD including the impaired extinction of fear memory. We first examined whether SPS changed the nuclear levels of GR in the rat hippocampus by Western blot, and found a significant increase 2 h after SPS. Subsequent analyses by ChIP-qPCR and RT-PCR revealed that SPS increased the binding of GR to the glucocorticoid response element (GRE) at the promoter of the Bcl-2 gene. Correspondently, we found the decreased expression of Bcl-2 mRNA in the hippocampus of SPS rats.
Based on these findings, it is plausible that the activation of hippocampal apoptotic pathway through the increased binding of GR to the GRE binding site may be induced by severe trauma, and may be consequently involved in the pathophysiology of PTSD. We are now examining the apoptotic changes in the hippocampus of SPS rats using TUNEL staining. In addition, we will examine the preventive effect of GR antagonist mifepristone (RU486) on the impaired fear extinction, changes in the hippocampal expression of apoptosis-associated genes, and the hippocampal apoptosis in SPS rats. Additional data will be shown at the meeting.

Disclosures: M. Araki: None. **M. Fuchikami:** None. **J. Omura:** None. **T. Miyagi:** None. **S. Morinobu:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.05/YY3

Topic: G.06. Post-traumatic Stress Disorder

Support: NSERC
Memorial Seed, Bridge and Multidisciplinary Grant

Title: Pre-conception predator stress induces physiological and behavioral changes in offspring

Authors: S. BHATTACHARYA, A1B3X9[1], A. FONTAINE[2], P. MACCALLUM[2], K. JARVIS[2], Q. YUAN[3], G. MARTIN[3], F. BAMBICO[4], *J. J. BLUNDELL[2]
[1]Psychol, Mem. Univ., St. John's, NL, Canada; [2]Psychol, [4]Psychology, [3]Mem. Univ., St John's, NL, Canada

Abstract: It is well known that traumatic stress can have deleterious effects on an individual. Recent data suggests that these harmful effects can propagate into future generations, making offspring more prone to mental illness (i.e. anxiety, depression and/or posttraumatic stress disorder). While recent data from the animal literature supports transgenerational effects of stress, little is known regarding the consequences of pre-conception stress on adolescent offspring. Furthermore, whether these changes persist into adulthood and make offspring more susceptible to future stressors is not known. Male and female mice were exposed to a predator (live rat-predator stress) or control condition for five minutes. Ten days later, stressed male mice were bred to stressed female mice and control male mice were bred to control female mice. On postnatal day (PND) 24, all offspring underwent a behavioural battery to assess anxiety-, depressive-like behaviour, and hyperarousal. We show that pre-conception predator stress increases anxiety-like behaviour as measured in the elevated plus maze, light/dark box, social anxiety test, and increased hyperarousal in adolescent offspring. At adulthood (PND 60), mice were subjected to a mild stressor and assessed for anxiety-, depressive-like behaviours, and hyperarousal. Pre-conception parental stress increased anxiety-like behaviour and hyperarousal in adult offspring exposed to a mild stressor indicating enhanced stress-susceptibility in these adult offspring. Furthermore, pre-conception parental stress increased stress-induced neural activation (cFOS expression), as well AMPA receptors (GLUA1), but not NR1, in the hippocampus of adult male offspring. Overall, our data suggest that traumatic stress not only affects an individual, but it can alter the behavioural responses of future generations. Currently, we are assessing the effects of pre-conception stress on the long-term potential in the hippocampus, hippocampal and amygdala dendritic morphology, corticosterone levels, and glucocorticoid receptors in offspring. Ultimately, identification of the mechanisms that promote anxiety in children, as well as increased stress-susceptibility in adulthood, will represent a major advance in the field, and may lead to novel treatments for such devastating, and often treatment-resistant disorders.

Disclosures: S. Bhattacharya: None. **A. Fontaine:** None. **P. MacCallum:** None. **K. Jarvis:** None. **Q. Yuan:** None. **G. Martin:** None. **F. Bambico:** None. **J.J. Blundell:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.06/YY4

Topic: G.06. Post-traumatic Stress Disorder

Support: 9261sc / W81XWH-13-2-0075

Title: Glutamatergic mechanisms mediate enduring vulnerability to drug use following an acute stressor

Authors: *C. GARCIA-KELLER[1], Y. KUPCHIK[2], C. MONFORTON[1], B. JACOBS[1], D. ROBERT-WOLFE[1], J. HEINSBROEK[1], L. M. CANCELA[3], P. W. KALIVAS[1]
[1]Neurosci., Med. Univ. of South Caroline, Charleston, SC; [2]Hebrew Univ. of Jerusalem, Jerusalem, Israel; [3]IFEC-CONICET. Dept Pharm. Sch. of Chem Sci. Nat Univ. of Cordoba, Cordoba, Argentina

Abstract: There is substantial evidence of comorbidity between stress disorders and substance use disorders (SUDs). Studies using a combined rodent model of stress and substance use reveal that previous exposure to stress predisposes animals to the behavioral effects of psychostimulants and opioids, including the development of behavioral sensitization and drug self-administration. Here we showed a remarkable overlap between the enduring neuroadaptations produced in nucleus accumbens core (NAcore) excitatory transmission after acute restraining stress and drug use. Specifically, we discovered that 3 weeks after a single acute stress (2 hr restraint) glutamatergic synapses on NAcore medium spine neurons (MSNs) show increased AMPA/NMDA ratio and dendritic spine density, and marked reduction in glial glutamate transporter (GLT-1) expression and function paralleling previous measurements made after withdrawal from cocaine. Besides, pairing a stressful event with a novel odor, we found that the stress-conditioned odor alone induced cocaine seeking, and potentiated seeking when paired with the cocaine-conditioned light/tone cue. Previous work revealed that cocaine seeking is prevented by restoring GLT-1 with N-acetylcysteine (NAC), and we found that 5-days treatment with NAC also prevented stress odor-induced cocaine seeking. Importantly, NAC treatment in humans alleviates cocaine craving and the symptoms of co-morbid SUDs/PTSD, indicating that the stress-induced adaptations we have identified may contribute to the neuropathology of comorbidity in humans.

Disclosures: C. Garcia-Keller: None. **Y. Kupchik:** None. **C. Monforton:** None. **B. Jacobs:** None. **D. Robert-Wolfe:** None. **J. Heinsbroek:** None. **L.M. Cancela:** None. **P.W. Kalivas:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.07/YY5

Topic: G.06. Post-traumatic Stress Disorder

Support: NIAAA U01 AA013498
NIAAA P60 AA006420
NIAAA T32 AA007456

Title: Sex differences in sensitivity to an unpredictable versus predictable stressor in a novel inhibitory avoidance-based rat model of comorbid alcohol and anxiety disorders

Authors: *M. Q. STEINMAN[1], D. KIRSON[1], S. A. WOLFE[1], S. R. SPIERLING[1], M. BAJO[1], S. SURESHCHANDRA[2], N. K. HOANG[1], A. SINGHAL[1], C. S. OLEATA[1], I. MESSAOUDI[2], E. P. ZORRILLA[1], M. ROBERTO[1]
[1]Dept. of Neurosci., The Scripps Res. Inst., La Jolla, CA; [2]Dept. of Mol. Biol. and Biochem., Univ. of California, Irvine, Irvine, CA

Abstract: Alcohol use disorder is often comorbid with anxiety disorders. These distinct conditions likely share common physiological etiologies that if elucidated could improve treatments for both alcoholism and anxiety. We adapted a recently published "2-hit" rat model of posttraumatic stress disorder (PTSD) to alcoholism research. Unlike more common alcohol footshock models, this model uses inhibitory avoidance to capitalize on both operant and Pavlovian fear conditioning. This is valuable as both types of responses occur in clinical anxiety disorders. In the model, 2 unpredictable footshocks administered once per day over 2 days promote long-lasting PTSD-like behavior. For unpredictable stress, each shock occurs in a different context (shuttle box vs. fear conditioning box) while predictable stress can be administered using the same shuttle box twice. We examined effects of unpredictable and predictable stress on alcohol intake during intermittent access 2-bottle choice (2BC) in male and female Wistar rats. In Experiment 1 rats were trained on 2BC for one month before shock exposure and were given 24 hr-long 2BC sessions. Predictable stress increased drinking in a subset of males that showed impaired inhibitory avoidance behavior during fear memory reactivation. Conversely, unpredictable stress caused a dramatic decrease in male 2BC drinking. We also examined translationally relevant PTSD-like behaviors. Male unpredictable stress rats exhibited enhanced acoustic startle responses. Both forms of stress disrupted sleep patterns in both sexes, shortening the longest bout of sleep. In Experiment 2 rats did not receive alcohol prior to footshock and the 2BC sessions were 2 hr-long to promote binge-like drinking. Stress increased alcohol intake in both sexes with the more potent treatment being predictable stress in males and unpredictable stress in females. Predictable stress males displayed a consistent

"deprivation effect" where they increased drinking after weekend abstinence. In all, these findings are consistent with reports that alcohol prior to footshock can impede the unpredictable shock-induced escalation in drinking. Ongoing studies are using the model to interrogate the role of neuroinflammatory responses in comorbid alcohol and anxiety disorders.

Disclosures: M.Q. Steinman: None. **D. Kirson:** None. **S.A. Wolfe:** None. **S.R. Spierling:** None. **M. Bajo:** None. **S. Sureshchandra:** None. **N.K. Hoang:** None. **A. Singhal:** None. **C.S. Oleata:** None. **I. Messaoudi:** None. **E.P. Zorrilla:** None. **M. Roberto:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.08/YY6

Topic: G.06. Post-traumatic Stress Disorder

Support: JSPS KAKEN Grant Number 25861006
JSPS KAKEN Grant Number 15K10729
JSPS KAKEN Grant Number 17K10273

Title: Beta-hydroxybutyrate attenuates anxiety-related behavior in rodent PTSD model

Authors: *T. YAMANASHI[1], M. IWATA[1], K. TSUNETOMI[1], N. KAJITANI[1], M. NAGATA[1], A. MIURA[1], R. MATSUO[1], T. NISHIGUCHI[1], R. S. DUMAN[2], K. KANEKO[1]
[1]Tottori Univ., Tottori, Japan; [2]Yale Univ. Sch. Med., New Haven, CT

Abstract: Post-traumatic stress disorder (PTSD) occurs after experiencing traumatic events such as war, disaster or violence. PTSD symptoms usually include intrusive recollections of traumatic events, avoidance of event reminders, anxiety and hyperarousal. Accumulated evidences have suggested that elevation of neuro-inflammation and decreased brain-derived neurotrophic factor (BDNF) contribute to the pathophysiology of PTSD. Recent reports show that in a rat model of PTSD, BDNF and CREB expression are decreased, and interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha) are increased in the hippocampus (Lee et al. 2018 J Nat Med). The absence of optimal treatments along with low response rates makes the investigation for novel pharmacological therapies a high priority. Beta-hydroxybutyrate (BHB) is a ketone body that supports mammalian survival during states of energy-deficit. Recent reports showed that BHB exerts an antidepressant effect in rodent models of depression by inhibiting neuro-inflammation (Yamanashi et al. 2017 Sci Rep) or increasing BDNF (Chen et al. 2017 Biochem Biophys Res Commun). In this study, we aimed to evaluate the possible beneficial effects of BHB in a rat PTSD model using single prolonged stress (SPS). On a single day, rats are subjected to a 2-hour immobilization followed immediately by a 20-min forced swim. Rats are given a brief period of recuperation and then subjected to diethyl ether until they are anesthetized

and unresponsive. After SPS, rats were administered BHB subcutaneously twice a day. After 1-2 treatment period, we evaluated anxiety behavior using an elevated plus maze test (EPM). We found that repeated BHB administration attenuates SPS-induced anxiety-related behavior. While additional studies are needed, these findings suggest that BHB may be a novel therapeutic candidate for the treatment of PTSD related anxiety symptoms.

Disclosures: T. Yamanashi: None. **M. Iwata:** None. **K. Tsunetomi:** None. **N. Kajitani:** None. **M. Nagata:** None. **A. Miura:** None. **R. Matsuo:** None. **T. Nishiguchi:** None. **R.S. Duman:** None. **K. Kaneko:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.09/YY7

Topic: G.06. Post-traumatic Stress Disorder

Support: DoD W81XWH-16-1-0016

Title: Transitional impairments in fear memory in rodent ptsd model that could be prevented by intranasal npy

Authors: *X. LIU, L. I. SEROVA, E. L. SABBAN
Dept. of Biochem. and Mol. Biol., New York Med. Col., Valhalla, NY

Abstract: Disruption of fear memory is one of the crucial features in posttraumatic stress disorder (PTSD). Neuropeptide Y (NPY) is an endogenous neuropeptide associated with resilience to PTSD. Using the single-prolonged stress (SPS) rodent PTSD model, we previously demonstrated that early intervention with intranasal NPY delivery to the brain prevented development of many neuroendocrine and behavioral abnormalities, included anxiety, hyperarousal, and depressive-like behavior. Here, we exposed rats to SPS stressors and immediately gave them intranasal NPY (SPS/NPY) or vehicle (SPS/V) and tested fear memory after one-week or two-weeks compared to unstressed controls.
One-week after SPS stressors, there was no difference among the groups in acquisition or extinction of contextual fear. But the retention session showed that the SPS/V, not the SPS/NPY group, had significantly enhanced retention of extinguished fear memory. In cued fear conditioning, the extinction retention also showed changes of freezing over time and the SPS/V rats exhibited significantly more freezing. Intranasal NPY prevented the enhanced fear memory in the SPS/V rats, and the SPS/NPY group exhibited similar freezing levels as the unstressed control group.
However, two-weeks after SPS stressors, the pattern of changes in fear memory was different and not elevated in the SPS/V group for retention of extinguished contextual fear. Similarly, with

cued fear conditioning, the SPS/V group did not show
enhanced freezing in the context used for extinguishing the tone. However, reinstatement by placing the rats back into the initial context paired with the tone stimulus without foot-shock revealed marked response in the SPS/V group. The data revealed two divergent SPS/V subgroups as determined by the D'Agostino and Pearson Omnibus Normality Test. One subgroup showed significantly enhanced fear memory and the other had reduced retention compared to unstressed controls.
Overall, our study demonstrated that SPS affected fear memory differently depending on progression of time subsequent to the exposure to the traumatic stress, and revealed individual differences in manifestation of the memory impairments after stress.

Disclosures: X. Liu: None. **L.I. Serova:** None. **E.L. Sabban:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.10/YY8

Topic: G.06. Post-traumatic Stress Disorder

Title: Determination of the relative reinforcing effect of MDMA by fixed ratio (FR) and progressive ratio (PR) intravenous self-administration testing in rats

Authors: *S. L. SMITH, M. HALLAM, D. HEAL
Renasci Ltd, Nottingham, United Kingdom

Abstract: There are relatively few published studies describing the reinforcing effects of MDMA (ecstasy) in rats. FDA recently granted breakthrough status to 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") for the treatment of PTSD. If MDMA is approved for medical use, it will have to move from being a C-I controlled drug to different schedules, i.e. C-II to C-V. There are very few published studies describing the reinforcing effects of MDMA in rats and none to our knowledge that have explored its relative reinforcing effect in this species. Therefore, we have investigated the reinforcing properties of MDMA in heroin-maintained rats using FR and PR schedules of drug reinforcement. Mildly food-restricted, male, Sprague-Dawley rats were initially trained to lever-press for food rewards before being surgically implanted with in-dwelling jugular catheters. Rats were allowed to self-administer heroin (15µg/kg/inj) on a fixed ratio (FR5) schedule of reinforcement in 2hr training sessions. After establishment of consistent heroin self-administration, the rats were subjected to saline extinction. The reinforcing effects of MDMA (0.025, 0.05, 0.1 or 0.25mg/kg/inj) were then evaluated on FR5 and FR3 schedules in 2hr sessions. In the second part of the experiment, if MDMA served as a reinforcer (>6 inj/session) in an individual rat, a 4hr progressive ratio (PR)/break-point analysis was performed. Results are mean ± SEM. Heroin maintained

self-administration in rats (15.6±2.2 inj/session, n=10) at levels significantly greater ($p<0.01$) than saline (4.9±0.3 inj/session, n=10). Although self-administration of MDMA was acceptable on FR5, it served as a more reliable reinforcer on FR3. On FR3, all doses of MDMA (0.025, 0.05, 0.1 or 0.25mg/kg/inj) maintained self-administration at levels significantly greater than saline (0.025=13.8±2.3 [n=4], $p<0.05$; 0.05=18.6±1.9 [n=5], $p<0.01$; 0.1=16.0±3.1 [n=5], $p<0.01$; 0.25=17.3±3.2 [n=5], $p<0.01$). The break-points for responding (mean lever-presses/inj) for these doses of MDMA were 18.0±2.9; 22.8±3.3; 20.0±2.2 and 30.6±7.4, respectively. MDMA served as a positive reinforcer across a 10-fold dose range in heroin-maintained rats. Powerful reinforcers, eg heroin (61.8±17.7, 25ug/kg/inj, n=8) and cocaine (65.7±22.2, 290ug/kg/inj, n=10) (Smith et al, 2016, SfN abst p.549.10) typically support break-points greater than 50 lever-press/inj. The break-point results obtained with MDMA classifies it as having moderate reinforcing efficacy in rats.

Disclosures: S.L. Smith: None. **M. Hallam:** None. **D. Heal:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.11/YY9

Topic: G.06. Post-traumatic Stress Disorder

Support: MRCSA Grant 77323

Title: Behavioral effects of a novel α_{2C}-adrenoceptor selective antagonist, ORM-10921, in an animal model of posttraumatic stress disorder (PTSD)

Authors: *D. WOLMARANS[1,2], C. L. ERICHSEN[2], D. J. STEIN[3,4], B. H. HARVEY[2,5]
[2]Ctr. of Excellence for Pharmaceut. Sci., [1]North-West Univ., Potchefstroom, South Africa; [3]Univ. of Cape Town, Cape Town, South Africa; [4]MRC Unit on Risk and Resilience in Mental Disorders, Cape Town, South Africa; [5]MRC Unit on Risk and Resilience in Mental Disorders, Potchefstroom, South Africa

Abstract: Posttraumatic stress disorder (PTSD) is a severe trauma and stress disorder that follows exposure to a life-threatening event in some individuals. Supported by clinical and pre-clinical data, dysfunctional noradrenergic signaling in the aftermath of trauma has been implicated. Current treatments for PTSD are inadequate and an urgent need exists to study the neurobiological constructs underlying the condition. While not overly successful, modulation of the noradrenergic system has attracted interest in the treatment of PTSD. In this regard, studies have suggested that non-selective modulation of the α_2 adrenoceptor exert opposing actions via the α_{2A} and α_{2C} receptors. Thus, the aim of the study was to explore the putative therapeutic effects of ORM-10921, a selective α_{2C}-adrenoceptor antagonist, in an animal model of PTSD, i.e.

predator scent exposure (PSE). 60 adult male Wistar rats (150 – 200g; 3-4 animals per cage) were randomly selected. Subjects were housed in ventilated cages that were maintained at 21ºC at a relative humidity of 50% on a 12-hour light-dark cycle (6h/18h). Food and water were provided ad lib (Ethical Clearance Nr NWU-00438-16-S5). Before the onset of experiments, subjects were randomly divided into non-scented and predator scent exposure cohorts. A single exposure (10 min) to a predator scented (normal cloth used as bedding material for a house cat for 3 months) or control cloth (normal cloth only; both 10 x 10 cm; one animal per cage) was applied. Immediately after exposure, subjects were divided into separate treatment groups (non-scented CTRL: n=8; non-scented ORM-10921: n=16; PSE CTRL: n=12; PSE ORM-10921: n=24) and injected with either saline or ORM-10921 (i.p.; 0.3 mg/kg/day) for 21 days. Our results indicate that PSE, but not exposure to non-scented cloth, induced significant anxiety-like behavior as assessed in the elevated plus maze (EPM) on day 7 post-exposure. Moreover, in congruence with the clinical condition in as far between-patient variance in post-trauma prognosis is concerned, this response could only be observed in 25% of the PSE cohort and lasted until day 21 post-PSE. With respect to the involvement of the α_{2C}-adrenoceptor in this behavior, ORM-10921 abrogated PSE-induced anxiety compared to CTRL animals as reflected by improvements in risk taking behavior and negligible changes in the number of open arm entries on day 7 vs 21 post exposure. In conclusion, this study can be appreciated as putative proof of concept for further investigations into the neurobiological role of the α_{2C}-adrenoceptor in anxiety-related conditions.

Disclosures: D. Wolmarans: None. **C.L. Erichsen:** None. **D.J. Stein:** None. **B.H. Harvey:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.12/YY10

Topic: G.06. Post-traumatic Stress Disorder

Support: DoD W81XWH-13-1-0377

Title: Female gonadal hormones during trauma may account for their higher risk of developing PTSD

Authors: *C. V. CHEN[1], I. LIBERZON[2]
[1]Univ. of Michigan, Ann Arbor, MI; [2]Psychiatry, Univ. of Michigan Hlth. Syst., Ann Arbor, MI

Abstract: Post-traumatic stress disorder (PTSD) is a deleterious mental health condition with a lifetime prevalence of 6-9% in the US, affecting twice as many women as men. Since gonadal hormones play a crucial role in many sex differences, they may contribute to sex differences in

the etiology and prevalence of PTSD in women. Using a PTSD rodent model, Single Prolonged Stress (SPS), our lab has shown that male rats exposed to SPS develop a deficit in retention of fear extinction, a postulated key deficit in PTSD. Here, we sought to determine how estrous cycle in female rats affect various aspects of fear associated learning like fear conditioning (FC), fear extinction (FE), and SPS-induced extinction recall (ER) deficits. The estrous cycle of adult intact female rats was tracked using vaginal swabs. Experimental groups were exposed to SPS during proestrus, estrus, diestrus 1 or diestrus 2; finally, all animals (controls included) were tested on FC, FE and ER. Findings indicate that, compared to controls, rats that experienced SPS acquire fear conditioning faster and, though they behave similarly during FE, show a deficit in retention of extinction. This deficit in SPS rats seems to be driven by animals that were in proestrus and estrus phases on the day of SPS. Estrus stage on the day of FC and FE did not seem to affect ER performance. In other words, being in proestrus or estrus on the day of trauma seemed to place female rats at a higher risk of developing extinction recall deficits, regardless of later hormonal stage during testing. Together, these data indicate that the higher prevalence in PTSD in women may be explained by the level of their endogenous gonadal hormones during a traumatic experience.

Disclosures: C.V. Chen: None. **I. Liberzon:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.13/YY11

Topic: G.06. Post-traumatic Stress Disorder

Support: DoD W81XWH-13-1-0377

Title: Role of adult hippocampal neurogenesis in SPS-induced extinction retention deficit

Authors: *E. RODRIGUEZ[1], J. A. GRECO[2], J. ABELSON[3], I. LIBERZON[4]
[1]Univ. of Michigan, Detroit, MI; [3]Psychiatry, [2]Univ. of Michigan, Ann Arbor, MI; [4]Psychiatry, Univ. of Michigan Hlth. Syst., Ann Arbor, MI

Abstract: Posttraumatic stress disorder (PTSD) has been functionally linked to impairments in context-dependent fear extinction retention (ER), a process that requires intact prefrontal cortex - hippocampal (Hpc) circuitry. PTSD patients show abnormalities in Hpc volume and function, and in contextual processing, generally. At the cellular level, adult Hpc neurogenesis plays a role in key Hpc functions, like pattern separation, and is sensitive to stress, but has not been examined in PTSD. Here we use an animal model of PTSD - single prolonged stress (SPS) - to examine adult Hpc neurogenesis and its involvement in context-dependent ER. We first demonstrated impaired ER in irradiated animals, associated with reduced Hpc neurogenesis (by

70%). Irradiated rats showed normal fear conditioning and fear extinction, but impaired ER (increased freezing) associated with the degree of immature cell loss within Hpc. Secondly, we examined the effects of SPS on neurogenesis, demonstrating decreased number of immature neurons in Hpc of SPS animals. To determine whether this effect was due to cell proliferation or survival, we injected BrdU (synthetic thymidine nucleoside, 5-bromo-2'-deoxyuridine) three weeks before SPS (cell survival) or one day after SPS (cell proliferation). In both cases, SPS reduced the number of BrdU+ adult-born dentate gyrus granule cells. Finally, we rescued SPS ER effects by enhancing Hpc neuronal survival - via environmental enrichment. Together, these data strongly support a role for adult Hpc neurogenesis in mediating an SPS-induced extinction retention deficit. These results identify neurogenesis as a potential mechanism underlying PTSD contextual processing deficits.

Disclosures: E. Rodriguez: None. **J.A. Greco:** None. **J. Abelson:** None. **I. Liberzon:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.14/YY12

Topic: G.06. Post-traumatic Stress Disorder

Support: VA National Center for PTSD

Title: Alterations in serum/glucocorticoid-regulated kinase transcript: Evidence for peripheral and CNS effects in PTSD

Authors: *B. LEE, M. J. GIRGENTI[1], B. HARE[1], M. S. MAZEI-ROBISON[2], R. S. DUMAN[1]
[1]Yale Univ. Sch. Med., New Haven, CT; [2]Physiol., Michigan State Univ., East Lansing, MI

Abstract: Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder with a life-time prevalence of 7.8% in the general population. Numerous studies suggest that alterations in gene transcription are associated with onset of PTSD. The majority of these studies have focused on peripheral blood transcript changes. While it is likely that many changes observed in the periphery reflect changes in the CNS, there are currently few studies directly examining the transcript changes in brain. In a previous study, we reported on the transcriptome analysis of postmortem brains of a small cohort of PTSD subjects, and identified serum/glucocorticoid regulated kinase 1 (*SGK1*) as being regulated in the dorsolateral prefrontal cortex (PFC). We have extended this work in a larger cohort of postmortem PTSD subjects and find that *SGK1* expression is decreased in the subgenual PFC. In addition, we find that levels of FK506 binding protein 5 (*FKBP5*), another gene implicated in PTSD based on studies of patient blood are also decreased in the subgenual PFC. Both genes are known to regulate inflammatory and glucocorticoid signaling. More importantly, previous studies in our lab have demonstrated that

Sgk1 inhibition enhances memory of contextual cues associated with fear conditioning. GWAS studies have identified 4 risk alleles within the *FKBP5* gene for development of PTSD. To further test the role of these genes identified from human samples in animal model of PTSD, we used classical fear conditioning in rats and found down regulation of both *Sgk1* and *Fkbp5* expression in medial PFC after training consistent with it's pattern of regulation in human subgenual PFC. Treatment with the synthetic glucocorticoid dexamethasone, in combination with one day of extinction training normalized levels of both transcripts in medial PFC and enhanced fear extinction. To better elucidate the functional consequences of decreased *Sgk1* expression on fear extinction, we are employing viral vector to express a catalytically inactive SGK1 protein into mPFC and measure extinction levels after training. These preclinical studies have identified *Sgk1* as a functionally important factor in the extinction of fear conditioning and support a role for dysregulation of this gene in the pathophysiology of PTSD and as a potential new target for therapeutic intervention.

Disclosures: B. Lee: None. **M.J. Girgenti:** None. **B. Hare:** None. **M.S. Mazei-Robison:** None. **R.S. Duman:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.15/YY13

Topic: G.06. Post-traumatic Stress Disorder

Support: TriService Nursing Research Program N16-P14
Center for the Study of Traumatic Stress

Title: Enhanced fear memory and regional brain glucose metabolism (FDG PET) following sub-anesthetic intravenous ketamine infusion in rats

Authors: *K. CHOI[1], K. RADFORD[2], T. PARK[3], S. JAISWAL[4], H. PAN[4], A. KNUTSEN[4], L. OSBORNE-SMITH[5], B. DARDZINSKI[6]
[1]Psychiatry, Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [2]Grad. Sch. of Nursing, [3]Psychiatry, [4]Ctr. for Neurosci. and Regenerative Med., Uniformed Services Univ., Bethesda, MD; [5]Nurse Anesthesia Program, Oregon Hlth. and Sci. Univ., Portland, OR; [6]CNRM, USUHS, Bethesda, MD

Abstract: Ketamine is one of the most commonly used battlefield analgesics administered to traumatically injured service members in Afghanistan. However, the impacts of peri-trauma administration of ketamine on the development of post-traumatic stress disorder (PTSD) are largely unknown. Moreover, there is a gap between pre-clinical and clinical studies because they utilize different doses and routes of ketamine administration. Therefore, we investigated the

effects of intravenous ketamine infusion on fear memory and *in vivo* regional brain glucose metabolism (BGluM) in rats. Male Sprague-Dawley rats received a continuous infusion of ketamine (0, 2, 10, and 20 mg/kg, 2 hr) either immediately after or 1 day after auditory fear conditioning (3 tone and footshock [0.6 mA, 1-sec] pairing). Fear memory retrieval, extinction, and recall were tested on days 2, 3, and 4 after fear conditioning and ketamine infusion. The effects of intravenous ketamine infusion (0 and 10 mg/kg, 2hr) on BGluM were measured using 18F-fluoro-deoxyglucose positron emission tomography (FDG PET) and computed tomography (CT). The ketamine infusion, both immediately after and 1 day after the fear conditioning, dose dependently enhanced fear memory retrieval, delayed fear extinction, and enhanced contextual and cued fear recall in rats. The ketamine infusion (10 mg/kg) increased BGluM in the hippocampus, amygdala, hypothalamus, and midbrain, while decreasing it in the cerebellum of rats. The current findings suggest that analgesic doses of ketamine infusion following stressful events may facilitate fear memory processing via activation of multiple brain regions that are critical for fear and stress. An additional research is in progress to understand molecular mechanisms of ketamine infusion on fear memory and BGluM.

Disclosures: K. Choi: None. **K. Radford:** None. **T. Park:** None. **S. Jaiswal:** None. **H. Pan:** None. **A. Knutsen:** None. **L. Osborne-Smith:** None. **B. Dardzinski:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.16/YY14

Topic: G.06. Post-traumatic Stress Disorder

Support: Work supported by Department of Psychology and College of Arts and Science at Miami University.

Title: Development of a mouse model of early life stress-enhanced fear learning

Authors: D. SCHLEICHER, J. J. QUINN, *A. K. RADKE
Psychology, Miami Univ., Oxford, OH

Abstract: Post-traumatic stress disorder (PTSD) is a serious and potentially debilitating disorder that can cause a range of cognitive, emotional, and behavioral issues. Previous studies have found that exposure to early life trauma increases an individual's likelihood of developing PTSD following subsequent trauma in later life (Kessler et. al., 2107). This study will attempt to model this phenomenon in a rodent population. To simulate early life trauma, this study adapted the early life stress-enhanced fear learning (SEFL) protocol of Quinn et. al 2014, which has proven successful in rats, to a novel mouse model. On postnatal day (PND) 17, male and female C57BL/6J mice were exposed to early life stress, which consisted of 15 foot shocks delivered

over the course of an hour, followed by a period of maternal separation. The mice were then allowed to reach maturity undisturbed. In adulthood (PND60-90), the mice underwent contextual fear conditioning (CFC) in a novel context. CFC consisted of a single foot shock delivered 180 seconds after the mouse had been introduced to the chamber. Freezing (a typical fear response of rodents marked by a lack of motion) was monitored and assessed during the first 180 seconds to establish a baseline fear level. The following day, the mice were re-introduced to the CFC context to test fear memory expression. During the test, freezing behavior was measured for a period of eight minutes, and no shocks were delivered. The test was performed each day for an additional three days, in order to measure the rate of extinction of the fear response. Following this, the same procedure was employed to evaluate fear memory expression in the original early life stress context. The results revealed that exposure to early life stress causes a significant enhancement of fear learning in male and female adult mice, significantly increasing the percent time spent freezing and prolonging the extinction process. Freezing was negligible during adult exposure to the early life stress context in all of the groups. This lack of memory for the early life stress context during adulthood suggests that enhancement of fear learning is not dependent on the associative memory of early life stress. The findings of this study agree with those of Quinn et. al 2014, providing evidence for the validity of the novel mouse model as well as the enduring and detrimental psychological impact of early life trauma.

Disclosures: D. Schleicher: None. **J.J. Quinn:** None. **A.K. Radke:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.17/YY15

Topic: G.06. Post-traumatic Stress Disorder

Support: DOD W81XWH-16-1-0016
Touro 49-506-1

Title: Single prolonged stress PTSD model triggers progressive severity of anxiety, sensitivity to NPY and alterations in gene expression in the hypothalamus

Authors: *E. L. SABBAN, L. I. SEROVA
Dept Biochem & Mol Biol, New York Med. Col., Valhalla, NY

Abstract: PTSD symptoms can be long-lasted or display delayed onset. Thus, it is important to take a staging approach which may reveal distinct therapeutic approaches according to the biological progression of the disorder. The single prolonged stress (SPS), widely used rodent model of PTSD, has been mostly studied one week after the traumatic stress. At this time point, we demonstrated that intranasal delivery of neuropeptide Y (NPY) to the brain could reverse the

anxiety and depressive-like symptoms. Here, we examined progression of PTSD related symptoms of anxiety and the ability for reversal by intranasal NPY as well as prolonged gene expression changes in the mediobasal hypothalamus. The percentage of rats with maximal anxiety index on EPM increased from 3.6% in controls, to 17.5% one week and 57.1% two weeks after the SPS stressors indicating delayed worsening of symptomatology and may provide a model of late-onset PTSD. A dose of intranasal NPY (150 μg/rat) which was able to reverse the symptoms after 1 week was ineffective after 2 weeks. At this time point, a single infusion with a double dose of NPY reversed anxiety and depressive-like behaviour to unstressed control levels. The temporal differences in sensitivity to NPY might be related to differences in activation of the HPA axis. Therefore, gene expression for NPY receptors, CRH, GR and FKBP5 were examined in the mediobasal hypothalamus 1, 2 and 4 weeks after SPS stressors. CRH mRNA levels were elevated the entire time. In contrast there was a flip in GR, FKBP5 and NPY receptor gene expression between 1 and 2 weeks post-SPS stressors. The mRNAs for GR and FKBP5 were increased over levels in unstressed rats after 1 week, but down regulated in the later stages with maximal alterations at 2 weeks. Y1R mRNA levels were unchanged, but mRNAs for Y2R and Y5R were markedly elevated after 1 week. At later times, only Y5R mRNA differed from unstressed levels, with barely half the levels in controls after 2 weeks and had returned to basal unstressed levels by 4 weeks. The results demonstrate that SPS elicits a time-dependent dysbalance between CRH/GR and NPY systems in the mediobasal hypothalamus. This may be involved in the delayed onset of severe anxiety which was overcome with higher dose of NPY.

Disclosures: E.L. Sabban: None. **L.I. Serova:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.18/YY16

Topic: G.06. Post-traumatic Stress Disorder

Support: 5R01NS052819

Title: BDNF Val66Met single nucleotide polymorphism enhances fear generalization in auditory fear conditioning

Authors: *N. TSE[1], J. D. RYAN[2], F. LEE[3]
[1]Weill Cornell Med. Grad. Sch. of Med., New York, NY; [2]Feil Family Brain & Mind Res. Inst., Weill Cornell Med., New York, NY; [3]Weill Cornell Med. Col., New York, NY

Abstract: Brain-derived neurotrophic factor (BDNF) is a key regulator in neuronal differentiation and synaptic plasticity. The human BDNF Val66Met single nucleotide polymorphism (SNP) leads to impaired activity dependent secretion of this growth factor, and

has been associated with an increased susceptibility to mood disorders such as depression and anxiety. In addition, BDNF Val66Met knock-in mice have been shown to have alterations in depression-like (forced swim test) and anxiety-like (open field, elevated plus maze) behaviors. However, no current studies have examined the BDNF Val66Met mouse in fear generalization, a behavioral process that is overactive in post-traumatic stress disorder (PTSD) and which inhibits the ability to distinguish between fearful cues and neutral cues. In this current study, we optimized a fear generalization paradigm and found that $BDNF^{Val/Met}$ mice display significantly increased fear generalization, as compared to wild-type controls. In particular, wild-type mice were able to distinguish between two distinct auditory cues, one of which is paired to a foot shock, while $BDNF^{Val/Met}$ mice displayed similar freezing times following both the fear and safety cues. These findings suggest that BDNF bioavailability is needed for the capacity to discriminate between cues associated with an aversive stimulus and neutral cues. Future studies will involve mechanistic gain of function studies to rescue this shift from discriminative to generalized fear in these variant BDNF SNP mice.

Disclosures: N. Tse: None. **J.D. Ryan:** None. **F. Lee:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.19/YY17

Topic: G.06. Post-traumatic Stress Disorder

Support: DA04483 EMU

Title: Vulnerability to traumatic stress predicts increased ethanol consumption in male and female rats

Authors: *R. R. DENNY[1], E. M. UNTERWALD[2]
[1]Ctr. for Substance Abuse, Temple Univ., Philadelphia, PA; [2]Dept Pharmacol & Ctr. Sub Abuse Res., Temple Univ. Sch. of Med., Philadelphia, PA

Abstract: Post-traumatic stress disorder (PTSD) begins with traumatic-stress exposure and is marked by frequent fear memory recollections and increased sympathetic nervous system arousal. Approximately 60% of males and 50% of females are exposed to at least one traumatic event during their lifetime. Only 15-30% of trauma-exposed individuals develop PTSD. PTSD is highly co-morbid with alcoholism and typically PTSD precedes the development alcoholism. The aim of the present study is to investigate the biological basis of susceptibility to this comorbidity using a rodent model. Male and female young adult Sprague-Dawley rats were exposed to a traumatic-stress using a single prolonged stress (SPS) model or control handling and were behaviorally phenotyped using responses on the elevated plus maze, open field test,

and cue reactivity. On the elevated plus maze, SPS-exposed males compared to controls had significantly lower % open arm time ($p < .05$) and SPS male and females had significantly lower % open arm entries compared to controls ($p < .05$), indicating higher anxiety-like behaviors in the SPS groups. Open field test and cue reactivity revealed no significant differences between group means of control versus SPS for males or females. Rats then underwent 6-12 weeks of intermittent two-bottle choice ethanol consumption. Correlation analyses between post-SPS behavioral endpoints and subsequent ethanol consumption in the male cohort revealed that cue reactivity (freezing to the tone) after SPS was a significant predictor of following ethanol consumption and mediated a large effect using the Pearson's r score ($p < .05$, $r > .5$). A significant predictor of female subsequent ethanol consumption was post-SPS elevated plus maze and mediated a large effect using the Pearson's r score ($p < .05$, $r > .5$). These data demonstrate that individual susceptibility to the traumatic stress as measured by higher anxiety-like behaviors in females and higher cue-reactivity in males predicts higher ethanol consumption. These findings will allow further investigation of the biological link between trauma-induced anxiety and ethanol consumption.

Disclosures: R.R. Denny: None. **E.M. Unterwald:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.20/YY18

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant 5R01NS052819

Title: Molecular and systems-level interrogation of the ventral hippocampus in mediating fear generalization

Authors: *J. D. RYAN[1], D. JING[2], N. TSE[3], F. LEE[2]
[1]Feil Family Brain & Mind Res. Inst., [2]Dept. of Psychiatry, [3]Grad. Sch. of Med. Sci., Weill Cornell Med., New York, NY

Abstract: Fear learning is an adaptive mechanism aimed at survival in the face of a potentially life-threatening threat that is conserved across species and is dependent on a classical conditioning process. Briefly, a cue (e.g., a tone) repeatedly paired with an aversive stimulus (e.g. electric shock) will induce a fear response independent of whether the shock is applied (which in rodents is exemplified by stereotyped immobility, or 'freezing'). Normally, animals display a robust ability to discriminate between cues associated with an aversive stimulus and neutral cues. If the aversive stimulus is particularly intense (to the degree that it might induce symptoms of PTSD in humans), then the animal will generalize and respond to both the fear cue

as well as neutral cues. However, the neural circuitry involved in mediating fear generalization remains unclear. Here, we use fiber photometry to measure population-level neural activity in the ventral CA1 (vCA1) region of the hippocampus in freely-moving mice during a fear memory retrieval task. We find that fear conditioning with a strong shock compared to a weak shock induces generalized freezing behavior and distinctive patterns of neural activity in the vCA1. We also find altered generalization behavior and neural signaling in BDNF Val66Met mice, indicating that altered activity-dependent BDNF secretion may contribute to fear generalization. Overall, this study provides insights into both the molecular mechanisms and neural circuits involved in fear generalization.

Disclosures: J.D. Ryan: None. **D. Jing:** None. **N. Tse:** None. **F. Lee:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.21/YY19

Topic: G.06. Post-traumatic Stress Disorder

Title: Pax7 neurons in the interpeduncular nucleus regulate fear memory

Authors: *J. LIANG, Y. REN, Q. FENG, M. LUO
Natl. Insitute of Biol. Sciences, Beijing, Beijing City, China

Abstract: The medial habenula (MHb)- interpeduncular nucleus (IPN) pathway has been preserved throughout evolution in vertebrates, suggesting that these nuclei may involve in very fundamental progresses for survival. Recently, some studies pointed out that MHb may have a role in fear regulation which is crucial since a proper response to danger often determines living or death. However, the neural mechanisms which MHb mediates such behaviors remain elusive. As the only downstream of MHb, the interpeduncular nucleus may be the proxy to relay fear signals from MHb to other related brain structures. Here, we used Pax7-creER mice which can specifically label almost the whole cells in IPN to investigate the role of this nucleus in fear regulation. By using fiber photometry and fear conditioning test, we found that IPN Pax7 neurons are activated by foot shock (US) and could learn a positive response to auditory cue (CS). Activation of IPN Pax7 neurons with channelrhodopsin (ChR2) increases freezing in the fear conditioning test whereas their ablation leads to a reduction of freezing. Taken together, these results may pave the way to understanding the behavioral function of this conserved but mysterious pathway and provide new insights to treat fear related neuropsychiatric disorders.

Disclosures: J. Liang: None. **Y. Ren:** None. **Q. Feng:** None. **M. Luo:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.22/YY20

Topic: G.06. Post-traumatic Stress Disorder

Support: NIMH Grant RO1MH105592

Title: Selective manipulation of BDNF promoter IV-expressing cells in the hippocampus modulates fear expression and hippocampal-prefrontal synchrony in mice

Authors: *H. QUILLIAN[1], H. L. HALLOCK[1], Y. MAI[1], J. L. HILL[2], K. R. MAYNARD[1], K. MARTINOWICH[1]
[1]Lieber Inst. for Brain Develop., Baltimore, MD; [2]Astellas Res. Inst. of America, San Diego, CA

Abstract: Our laboratory has previously shown that mice with disrupted production of brain-derived neurotrophic factor (BDNF) from promoter IV (p4) have impaired fear expression and extinction that co-occurs with decreased oscillatory synchrony between the hippocampus (HPC) and medial prefrontal cortex (mPFC). These results suggest that activity-dependent BDNF signaling critically regulates HPC-mPFC communication, which is associated with a variety of fear and anxiety-related behaviors. To better understand how p4-expressing cells in the HPC-mPFC circuit regulate fear expression and HPC-mPFC synchrony, we designed a viral construct that selectively targets these cells for tamoxifen inducible Cre-mediated recombination (AAV8-p4Bdnf-ERT2CreERT2-PEST-P2A). Injection of this construct, along with a virus encoding for Cre-dependent expression of tdTomato, into the HPC of wild-type (WT) mice successfully induced tamoxifen-mediated labeling of p4-expressing cells. Using the p4CreERT2 construct, we next induced expression of an excitatory Designer Receptor Exclusively Activated by Designer Drugs (DREADD), hM3Dq, in p4-expressing cells located in the ventral HPC of WT mice. Synthetic activation of these neurons with clozapine-N-oxide (CNO) increased fear expression during both pre-tone context recall and within-session tone/context extinction, as measured by percentage of time spent freezing while in the conditioning chamber. *In vivo* recording of local field potentials (LFPs) in the ventral HPC and mPFC revealed reduced HPC-mPFC oscillatory synchrony and altered power spectra in hM3Dq+ mice during fear recall and extinction. These effects were not due to non-specific alterations in behavior or brain activity following activation of these cells, as no significant differences in behavior or LFP activity were observed between groups in the home cage following CNO injections. Our data reveal a critical role for BDNF p4-expressing cells in the ventral HPC and hippocampal-prefrontal synchrony during fear-related behavior. We propose that normal activation of p4-expressing HPC cells in the hippocampal-prefrontal pathway promote optimal fear expression. The data also demonstrate the utility of our

p4CreERT2 construct for selectively targeting genetically-distinct populations of cells to better understand their contribution to HPC-mPFC circuity and fear-related behavior.

Disclosures: H. Quillian: None. **H.L. Hallock:** None. **Y. Mai:** None. **J.L. Hill:** None. **K.R. Maynard:** None. **K. Martinowich:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.23/YY21

Topic: G.06. Post-traumatic Stress Disorder

Support: NIMH Grant RO1MH105592

Title: Regulation of fear expression by activity-dependent BDNF in direct hippocampal-to-prelimbic projections

Authors: *H. L. HALLOCK[1,2], J. L. HILL[4], Y. MAI[2], H. M. QUILLIAN, IV[2], H.-Y. CHEN[3], G. R. HAMERSKY[5], B. J. MAHER[2], K. MARTINOWICH[2]
[1]Baltimore, MD; [3]Developmental Electrophysiology, [2]Lieber Inst. for Brain Develop., Baltimore, MD; [4]Astellas Pharma, San Diego, CA; [5]Developmental Electrophysiology, Lieber Inst., Baltimore, MD

Abstract: Fear dysregulation is a hallmark symptom of several neuropsychiatric disorders, including generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD). Both the hippocampus and medial prefrontal cortex (mPFC) have been linked with expression of learned fear in rodents, but the mechanisms by which these brain regions regulate fear memory remain poorly understood. To identify the contribution of hippocampal-prefrontal signaling to the recall and expression of learned fear, we demonstrate that direct inputs from ventral hippocampal CA1 (vHC) to the prelimbic subregion of the mPFC (PrL) are selectively recruited during fear expression in wild-type (w/t) mice. We also show that activation of vHC-PrL projectors with an excitatory designer receptor exclusively activated by designer drugs (DREADD) reduces fear expression during both context recall and within-session extinction, and disrupts freezing-related population dynamics in PrL neurons. To probe the molecular events that regulate function in this circuit during fear expression, we tested fear recall in mutant mice with disrupted production of brain-derived neurotrophic factor (BDNF) from activity-dependent promoter IV (-e4 mice), and found that these mice had increased expression of learned fear relative to w/t controls. We next used a combination of viral targeting and single-molecule fluorescence *in situ* hybridization to show that a similar proportion of vHC-PrL projectors are activated during fear expression in both w/t and –e4 mice, and co-express high levels of both exon IV-containing *Bdnf* and *Ntrk2* (which encodes the TrkB receptor) transcripts following fear

recall in both genotypes. Whole cell patch clamping recordings in *ex vivo* slice preparations revealed that vHC-PrL projectors in –e4 mice receive a lower frequency of inhibitory post-synaptic currents (iPSCs), and have a more depolarized resting membrane potential at baseline, relative to w/t projectors. These results suggest that activation of projectors in the absence of promoter IV-derived BDNF may lead to increased fear expression. In support of this hypothesis, synthetic activation of these neurons in –e4 mice led to an opposite phenotype than that observed in w/t mice (increased fear expression during recall and extinction). Taken together, these data support the central hypothesis that activity-dependent BDNF signaling impacts the ability of vHC-PrL projectors to bi-directionally regulate fear expression. Targeting clinically-relevant signaling pathways in defined neural circuits could provide avenues for precision medicine approaches to treating disorders that feature fear dysregulation.

Disclosures: H.L. Hallock: None. **J.L. Hill:** None. **Y. Mai:** None. **H.M. Quillian:** None. **H. Chen:** None. **G.R. Hamersky:** None. **B.J. Maher:** None. **K. Martinowich:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.24/YY22

Topic: G.06. Post-traumatic Stress Disorder

Support: FAPESP - 2017/10484-6
PROEX-CAPES
CNPq

Title: Behavioral effects of early life stress in the predator confront model of PTSD

Authors: *N. COBRA BARREIRO BARROCA[1], E. H. LIMA UMEOKA[1], M. SANTOS DA SILVA[2], J. ANTUNES-RODRIGUES[2], M. F. JURUENA[1], N. CYSNE COIMBRA[1], N. GARCIA-CAIRASCO[2]
[1]Dept. of Neurosci. and Behavioral Sci., [2]Dept. of Physiol., Univ. of São Paulo, Ribeirao Preto, Brazil

Abstract: Stress during early life is associated with a higher risk of developing psychopathologies in adult life, for example, post-traumatic stress disorder (PTSD), a psychopathology triggered by a traumatic event and characterized by intense anxiety, avoidance and hypervigilance. It reflects stress-induced changes in neurobiological systems and an inadequate response of them against re-exposure to the context of the trauma. The aim of this study was to assess if stress experienced during early periods of postnatal development, is related to a greater defensive response later in life, in a PTSD model.Mice were subjected to the limited bedding and nesting model of early life stress (ELS) from P2 to P9, which induces abnormal and

fragmented maternal care. One batch of mice was sacrificed at P9, body weight and corticosterone (CORT) were determined. Another batch was allowed to reach adulthood, and at P120, submitted to predator confront paradigm, using exposure to a venomous snake (*Bothrops moojeni*) and re-exposure to its skin a week later, in the same experimental context. Frequency and time spent at risk assessment, escape, defensive immobility and interaction with predator (exposure) or with the skin (re-exposure) were determined.At P9 ELS mice, compared to controls, presented significantly reduced body weight (2.75 ± 0.13 g, n=21 and 3.89 ± 0.09 g, n=33; $p<0.001$) and increased CORT basal levels (5.41 ± 1.32 µg/dl, n=21 and 2.63 ± 0.18 µg/dl, n=26; $p<0.05$). At P120, during predator exposure, ELS mice spent significantly more time in scape (4.8 ± 2.19 %, n=9 and 1.93 ± 1.03 %, n=6; $p<0.05$) and interaction (0.66 ± 0.45 %, N=9 and 0.18 ± 0.30 %, N=6; $p<0.05$) behaviors compared to control group. During re-exposure, regardless of the ELS experience, females had significantly enhanced frequency of risk assessment and escape ($p<0.05$). Moreover, ELS males showed increased frequency and time for escape during re-exposure ($p<0.05$), when compared to those mice confronted with the predator. It was also observed main effect of ELS ($p<0.05$) on the number of risk assessment and interaction between prey and predator, in comparison to control mice, for those without previous exposure to the predator.ELS induced physiological changes leading to alterations in PTSD-like behaviors in the prey versus predator confrontation model during adult life. Detailed behavioral analysis associated with an anatomical determination of Fos+ neuronal activity in key brain structures should provide further insights on the role played by ELS on the neurobiology of psychiatric disorders, such as PTSD and panic attacks, as well as other unconditioned/conditioned fear- and anxiety-related conditions.

Disclosures: N. Cobra barreiro barroca: None. **E.H. Lima Umeoka:** None. **M. Santos Da Silva:** None. **J. Antunes-Rodrigues:** None. **M.F. Juruena:** None. **N. Cysne Coimbra:** None. **N. Garcia-Cairasco:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.25/YY23

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant DA031900

Title: Susceptibility and resilience to predator odor stress differs between male and female rats

Authors: *E. M. BLACK[1], Z. D. BRODNIK[2], N. W. SNYDER[3], J. R. BARSON[1], R. A. ESPAÑA[1]
[1]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Drexel Univ., Philadelphia, PA; [3]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"). Further, data from human studies suggest that women are up to twice as likely as men to meet criteria for PTSD. Although many studies have examined behaviors in PTSD models in male rats, data is still lacking with regard to the behavioral and neurobiological response of female rats in these models. We employed our previously established predator odor stress model of PTSD to classify and define the neurobiological and behavioral correlates of female rats in response to predator odor exposure. The importance of such an approach was highlighted by the divergence from cut-off criteria established in male rats. Unlike male rats, segregation into susceptible and resilient groups in female rats was primarily influenced by hypervigilance as measured by acoustic startle response. Females in this model also demonstrated increased locomotion in anxiety-prone environments and alterations in corticosterone levels that differed from those observed in males, suggesting unique responses to predator odor stress. Interestingly, the prevalence of susceptibles is markedly similar between male and female rats. Thus, though males and females may differ in some anxiety-related physiological and behavioral responses in the predator odor stress model of PTSD, the overall likelihood of displaying the PTSD-phenotype is similar between the sexes. This research emphasizes the importance of establishing unique and appropriate segregation criteria for males and females in order to properly characterize sex differences in the field of stress research.

Disclosures: E.M. Black: None. **Z.D. Brodnik:** None. **N.W. Snyder:** None. **J.R. Barson:** None. **R.A. España:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.26/YY24

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant R15NS078645
BYU MEG

Title: True prophylactic treatment effect in a rat PTSD model on plasticity in ventral hippocampal, lateral amygdala, and medial prefrontal cortex and molecular targets

Authors: *R. M. MILLER[1], E. SAITO[2], B. DABNEY[2], R. HANSEN[2], G. MELENDEZ[2], S. M. PICKARD[2], C. EDWARDS[2], L. APONIK[2], T. CROFTS[2], S. MANGUM[2], J. G. EDWARDS[1]
[1]Physiol. and Developmental Biol., [2]Brigham Young Univ., Provo, UT

Abstract: Post-traumatic stress disorder (PTSD) is a complex anxiety/depression disorder that affects about 1 out of 4 individuals after a stressful/traumatic experience. Two commonly used models that we employed were single prolonged stress (SPS) and social defeat (SD) (both used with 2 weeks of chronic light). First, more naturally anxious rats were selected based on results of an open field test where cat fur and fox urine were placed in one quadrant. Rats were classified as anxious if they avoided that quadrant, froze for long periods of time, did not rear, and frequently urinated or defecated. The naturally anxious rats were used in either the SPS or SD protocols. Next, the elevated plus maze (EPM) and light-dark transition (LDT) tests were used to detect anxious behavior at the conclusion of SPS or SD protocols. We noted that both protocols were able to cause significant anxious behavior when compared to controls, with SD being more significant. Next, we performed field electrophysiology experiments in rat brain slices. The data illustrated that the SD protocol caused significant changes in ventral hippocampus plasticity while SPS did not. Therefore, we used the SD model to look at changes in other brain regions known to have altered plasticity in PTSD. SD caused a significant increase in long-term potentiation (LTP) in the ventral hippocampus (VH), lateral amygdala (LA), and medial prefrontal cortex (mPFC). To determine whether a prophylactic treatment could prevent the physiological changes of PTSD, we simultaneously administered propranolol and mifepristone at 10 mg/kg doses by intraperitoneal injection one week prior and during the entire duration of SD. These drugs significantly decreased LTP in the VH, LA, and mPFC of SD rats that received drug injections when compared to SD rats with no drug injections and controls. However, the SD drug treated rats did not show significant reductions in anxious behavior when tested on the EPM and LDT when compared to the SD rats with no drug injections and still exhibited significantly more anxious behavior than control rats. We then examined potential gene targets involved in plasticity and stress that could be altering the LTP in stressed and drug-treated rats. Significant alterations in the mRNA expression levels of glucocorticoid, mineralocorticoid, and beta 3 adrenergic receptors; AMPAR subunits, and NMDAR subunits were detected using RT-qPCR between all groups in all three brain regions. Overall, our data suggest that propranolol and mifepristone together may be a viable prophylactic treatment for preventing PTSD.

Disclosures: R.M. Miller: None. **E. Saito:** None. **B. Dabney:** None. **R. Hansen:** None. **G. Melendez:** None. **S.M. Pickard:** None. **C. Edwards:** None. **L. Aponik:** None. **T. Crofts:** None. **S. Mangum:** None. **J.G. Edwards:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.27/ZZ1

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant 5R21MH109945-02

Title: Differential baseline and activity-dependent transcriptional profiles between modifiable and modification-resistant memories

Authors: *J. M. PERISH, A. SANDOVAL, H. ELAHI, J. PLOSKI
The Univ. of Texas at Dallas, Richardson, TX

Abstract: The repeated, involuntary recall of traumatic experiences in anxiety disorders such as post-traumatic stress disorder (PTSD) is tremendously distressing to patients and presents a technical challenge to neuroscientists. After initial storage, long-term memories can be retrieved, modified, and re-stabilized in a related process called reconsolidation updating. Existing research suggests reconsolidation updating is an adaptive process allowing formerly consolidated long-term memories to be modified. Numerous studies have demonstrated that circuits encoding weak fear memories become destabilized after retrieval necessitating the protein synthesis-dependent process of reconsolidation to re-stabilize the memory and, thus, allow its permanence. This period of lability presents a potential therapeutic window whereby memory re-stabilization can be pharmacologically disrupted to induce amnesia. Strong, pathological memories (as in PTSD), however, are resistant to reconsolidation initiation. This limits the potential clinical utility of reconsolidation therapy as a means to attenuate pathological memories. The largest obstacle to development of a targeted reconsolidation therapy is an insufficient understanding of the molecular mechanisms gating reconsolidation initiation for strong fear memories. Existing therapies have been largely ineffective in attenuating PTSD-related symptomologies. It is critical we study the molecular biological differences of modifiable versus modification-resistant fear memories to aid the development of an effective PTSD treatment. Here, utilizing Next Generation Sequencing technology, we demonstrate the baseline and retrieval-dependent transcriptional differences between amygdalae encoding modifiable and modification-resistant fear memories and propose experiments to further elucidate the molecular mechanisms impeding reconsolidation of strong fear memories.

Disclosures: J.M. Perish: None. **A. Sandoval:** None. **H. Elahi:** None. **J. Ploski:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.28/ZZ2

Topic: G.06. Post-traumatic Stress Disorder

Support: VA I01 BX001978
VA I01 BX003890
NSF IOS 1258111

Title: Sex differences in revealing susceptibility to a PTSD-like phenotype in rats (RISP model)

Authors: D. CRETHERS[1], K. ALEXANDER[1], R. NALLOOR[2], K. BUNTING[1], *A. I. VAZDARJANOVA[2]
[1]Augusta Univ., Augusta, GA; [2]Charlie Norwood VA Med. Ctr., Augusta, GA

Abstract: We have previously demonstrated that we can reveal individual susceptibility to a Post-Traumatic Stress Disorder (PTSD)-like phenotype (RISP model) in male rats. Revealing susceptibility requires exposure to a mild stressor and subsequent characterization of the rats' startle response to a series of loud white noise presentations (ASR) and anxiety-like behavior in the Elevated Plus Maze. According to the RISP model, rats high on both measures are classified as susceptible (Sus), while those low on both measures- resistant (Res). The RISP model has both face and predictive validity, as Sus male rats account for ~20% of the tested population similar to the percentage reported for men who develop PTSD after exposure to a traumatic event. Additionally, after exposure to an emotionally traumatic event (high footshock in a novel place or contextual fear conditioning) Sus, compared to Res, rats show impaired fear extinction, elevated startle for nearly a month after the trauma, generalized anxiety, and impaired performance on a task requiring cognitive flexibility. All of these behaviors map to diagnostic criteria for PTSD (DSM-V). Accordingly, Sus rats also have impaired hippocampal and medial prefrontal cortical function compared to Res rats, as revealed by task-induced expression of plasticity-associated genes (*Arc* and *Homer 1a*). These brain regions are required for successful fear extinction and cognitive flexibility and contribute to altered anxiety-like behavior. Importantly, their function is disrupted in people with PTSD. PTSD is a sexually dimorphic condition with females suffering at twice the rate of men. Therefore, we hypothesized the RISP model will identify a higher percentage of female rats as Sus. We discovered that identifying susceptibility in females requires a different set of criteria. While the pre-trauma ASR and anxiety-like behavior were positively correlated in males, in females, this correlation was negative. Furthermore, the post-trauma behavior in females was significantly different than males: impaired fear extinction was not correlated with post-trauma ASR. These data demonstrate that a PTSD-like phenotype as well as susceptibility to such a phenotype should be modeled differently in males and females. It also cautions that making translational inferences from animal research done only in males may apply better to men than women suffering from PTSD.

Disclosures: D. Crethers: None. **K. Alexander:** None. **R. Nalloor:** None. **K. Bunting:** None. **A.I. Vazdarjanova:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.29/ZZ3

Topic: G.06. Post-traumatic Stress Disorder

Support: Military Operational Medicine Research Program, US Army Medical Research and Materiel Command

Title: Modulation of associative learning and reflexive behavior depends on timing of administration of the fatty acid amide hydrolase (FAAH) inhibitor URB597

Authors: *E. G. LOWERY-GIONTA[1], L. P. SIMMONS[2], E. BERGMAN[3], M. ETUMA[3], N. L. MOORE[4]
[1]Ctr. for Military Psychiatry and Neurosci., Walter Reed Army Insitute of Res., Silver Spring, MD; [2]Walter Reed Army Inst. of Res., Burtonsville, MD; [4]Ctr. for Military Psychiatry and Neuroscience, Behavioral Biol. Br., [3]Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Impairments in associative learning are found in post-traumatic stress disorder (PTSD). Previous reports of the involvement of the endocannabinoid system in associative memory processes suggest compounds influencing this system may assist in recovery from adverse behavioral responses to fear memories. To better understand the role of endocannabinoid tone in fear-associated learning and memory, we characterized the impact of the FAAH inhibitor URB597 in a rodent model of fear conditioning and conditioned suppression of food-maintained operant behavior. To better distinguish conditioned suppression from freezing behavior, an ongoing study is examining the effects of URB597 on freezing behavior alone. Male rats were initially trained and subsequently maintained on a variable-interval schedule of reinforcement (VI32) in food-maintained operant sessions. Following this, rats were conditioned to associate light-and-tone pairing to an aversive footshock (i.e., conditioning, "IES") and later tested for conditioned suppression of lever-pressing (i.e., extinction, "EXT"). URB597 (0.1 or 0.3 mg/kg, i.p.) or its vehicle was administered 30-min prior to either IES or EXT to assess effects of FAAH inhibition on the acquisition and expression/extinction of conditioned fear responses, respectively. One week after EXT tests, light-potentiated startle responses were measured. In a separate ongoing study, the effects of URB597 (0.1 or 0.3 mg/kg, i.p.) given during IES or EXT on fear-associated freezing behavior is being assessed. At the tested doses, URB597 administered in either the IES or EXT phase of the study resulted in non-significant decreases in the latency to the first active-lever press following a single light-and-tone cue delivery relative to control groups. This effect was most obvious on the first of five days for either IES or EXT phases, and all groups were indistinguishable by the third day. Interestingly, URB597 (0.3 mg/kg) administered in the IES phase resulted in significantly greater potentiation of light-potentiated startle relative to the EXT-administered group. This suggests that administration of URB597 could enhance conditioned fear learning if given when the conditioned fear association is acquired. Thus, careful consideration of the timing of administration of a cannabinoid compound should be made as the potential therapeutic value of such compounds are evaluated for the treatment of PTSD and related disorders. Ongoing studies of URB597's effects on freezing behavior will provide additional insights in to the effects of cannabinoid modulators on conditioned fear processes.

Disclosures: E.G. Lowery-Gionta: None. **L.P. Simmons:** None. **E. Bergman:** None. **M. Etuma:** None. **N.L. Moore:** None.

Poster

682. Post-Traumatic Stress Disorder: Preclinical Models

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 682.30/ZZ4

Topic: G.06. Post-traumatic Stress Disorder

Support: MOMRP

Title: Reflexive, exploratory, and learning behavior characterization of nociceptin/orphanin FQ (NOP) receptor antagonists in a rodent model of traumatic stress

Authors: *R. M. ENGA, E. M. BERGMAN, I. H. JEONG, M. D. MAY, M. C. VENTURA, N. L. T. MOORE
Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Current FDA-approved pharmacotherapies for treatment of post-traumatic stress disorder (PTSD) are limited in number and can be inefficacious, leaving a need for characterization and evaluation of other possible pharmacotherapies. Rodent models of traumatic stress have been established, including underwater trauma and predator (PRED) exposure. Recent evidence implicates the nociceptin/orphanin FQ (NOP) receptor system in PTSD, including a single-nucleotide polymorphism within the OPRL1 gene encoding the NOP receptor and effects of NOP agonist/antagonist on centrally-mediated processes known to be impaired in PTSD. Here, we first characterized the effects of two NOP antagonists on baseline behavioral performance in rats. Subsequent, ongoing studies are examining the effects of NOP antagonism on behavioral recovery after traumatic stress exposure as well as on Pavlovian fear conditioning. Male rats were administered J-113397 (2-20 mg/kg, i.p.), SB-612111 (0.1-4 mg/kg, i.p.), or vehicle once-daily and tested in behavioral performance in acoustic startle response (ASR), elevated plus maze (EPM), hot plate test, and open field (OF). Tests were performed on Days 1, 2, and 7 to assess acute and repeated administration effects. In a subsequent, ongoing study, these NOP antagonists are undergoing evaluation for their efficacy on behavioral performance recovery one or seven days following protected exposure to a single-day 3-species predator (snake, ferret, and cat) exposure regimen or sham exposure. Finally, an additional ongoing study is evaluating the efficacy of the NOP antagonist, JTC-801 (1-10 mg/kg, i.p.), on reducing fear-associated freezing behavior after an initial conditioning session in which a mild, brief footshock is paired with co-terminating light and tone cues. The NOP antagonists J-113397 and SB-612111 did not significantly affect baseline behavioral performance in ASR, EPM, hot plate test, or OF at any tested dose. This suggests a lack of behavioral effect of these NOP antagonists on the critical behavioral measures used to characterize our rodent models of traumatic stress in stress-

naïve rodents. Ongoing studies will determine the efficacy of NOP antagonism on behavioral recovery following predator exposure as well as on fear conditioning.

Disclosures: R.M. Enga: None. **E.M. Bergman:** None. **I.H. Jeong:** None. **M.D. May:** None. **M.C. Ventura:** None. **N.L.T. Moore:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.01/ZZ5

Topic: G.07. Other Psychiatric Disorders

Title: Modulation of hippocampal gamma oscillations by amphetamine and guanfacine

Authors: B. H. DENNIS[1], F. WEISZ[2], A. BRITO DA SILVA[3], M. O. CUNNINGHAM[3], S. A. NEALE[1], *T. E. SALT[2,1]
[1]Neurexpert Ltd, Newcastle-upon-Tyne, United Kingdom; [2]UCL Inst. Ophthalmology, London, United Kingdom; [3]Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: Neuronal circuit oscillations in the neocortex and hippocampus are thought to underly a number of functions related to learning, attention, and cognition. Within the hippocampus, gamma-frequency oscillations, are important in the routing of information and thus attention and memory formation. *Gamma* oscillations are thus thought to be an important biomarker of cognitive functions. Amphetamine and guanfacine are drugs that are known to modulate cognitive performance in animals and humans, albeit via different mechanisms, and have been used to treat conditions such as ADHD. We therefore investigated the actions of these drugs on hippocampal *gamma* oscillations in order to shed further light on their potential mode(s) of action.
Horizontal *in vitro* slice preparations (450μm thickness) were made from the brains of adult male Sprague-Dawley rats. Extracellular field recordings were made from the CA3 area of the hippocampus in an interface bath at ~33C. Addition of carbachol (Cch; 5μM) to the bathing medium resulted in the generation of stable *gamma* oscillations with peak power in the 32-60Hz region. Addition of D-amphetamine to the bathing medium (10μM, 15 minute application) in the continued presence of Cch resulted in changes in the power spectrum, such that there was an overall increase in power and the peak in the spectrum shifted to the 10-20Hz ("*beta*") range (from 34.8±3.1Hz to 7.8±8.5Hz, mean±Std Dev, *n*=7). This was associated with the occurrence of high-amplitude sharp wave activity. Similar, more pronounced, effects were also seen in the presence of 100μM D-amphetamine. By contrast, addition of guanfacine (10μM) to the bathing medium had little effect on the peak frequency in the power spectrum, but decreased the *gamma*-frequency power to 66±6.3% (*n*=5) of control.
Amphetamine is thought to exert its effects (at least in part) via dopaminergic mechanisms,

whereas guanfacine is an *alpha*2A- adrenoceptor agonist. Our finding that they have different actions on hippocampal circuit function emphasises this difference and may be important in characterising the actions and mechanism of action of other potential drugs developed for attention and cognitive disorders.

Disclosures: B.H. Dennis: None. **F. Weisz:** None. **A. Brito Da Silva:** None. **M.O. Cunningham:** None. **S.A. Neale:** None. **T.E. Salt:** A. Employment/Salary (full or part-time):; Neurexpert Ltd.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.02/ZZ6

Topic: G.07. Other Psychiatric Disorders

Title: Gene expression analysis of ASD patients using LCLs

Authors: *M. TORITSUKA[1], M. MAKINODAN[1], T. YAMAUCHI[1], Y. YAMASHITA[1], D. IKAWA[1], T. KOMORI[1], S. KIMOTO[1], K. HAMANO-IWASA[1], R. TAKADA[1], A. OMORI[1], E. SUMIDA[1], H. KITAOKA[1], M. HONDA[1], H. MATSUZAKI[2], T. KISHIMOTO[1]
[1]Dept. of Psychiatry, Nara Med. Univ., Kashihara, Japan; [2]Univ. of Fukui, Eiheiji-Cho, Yoshida-Gun, Japan

Abstract: Objective; Lymphoblastoid cell lines (LCLs) are nearly-immortalized B cells developed by infecting peripheral blood lymphocytes with Epstein-Barr virus, which provide a long-lasting supply of cells as a biological resource. These cells have been utilized not only for genome sequencing, but also for phenotypic analyses of cells from subjects with neuropsychiatric disorders, such as autism spectrum disorder (ASD). The pathobiology of ASD is considered to be associated with aberrant immune activation, such as increased levels of plasma pro-inflammatory cytokines, and excessively activated microglia as observed by positron emission tomography scanning. An immune cell in the brain is microglia having the same origin with peripheral macrophages, but direct analysis of microglia is impossible because of its inaccessibility. Our recent studies highlighted the usefulness of peripheral blood cells instead of the microglia, thus we aimed this study to identify biomarkers of ASD using LCLs as a substitute for microglia. Methods; We evaluated the gene expression of LCLs established from ASD patients and typically developed (TD) children by qRT-PCR. All study participants and their legal guardians provided written informed consent prior to enrollment. This study was approved by the appropriate Ethics Committee of the Nara Medical University and was performed in accordance with the Declaration of Helsinki. Results; To verify the stability of the cellular features of newly established LCLs, we first measured gene expression in LCLs of TD group with different passage numbers. The result showed that gene expression substantially changed

within 10 passages in LCLs, and, in particular, the expression of *GAPDH*, a common house-keeping gene used as internal control for qPCR, varied considerably during subculture. Next we compared gene expression of pro-inflammatory cytokines between ASD and TD. Surprisingly, the expression of some of them were lower in ASD group. Conclusion; Our data suggest that the use *GAPDH* as an internal control for qRT-PCR may be unsuitable when using early passage LCLs, and that LCLs can be a useful tool for searching biomarkers of neuropsychiatric disorders.

Disclosures: M. Toritsuka: None. **M. Makinodan:** None. **T. Yamauchi:** None. **Y. Yamashita:** None. **D. Ikawa:** None. **T. Komori:** None. **S. Kimoto:** None. **K. Hamano-Iwasa:** None. **R. Takada:** None. **A. Omori:** None. **E. Sumida:** None. **H. Kitaoka:** None. **M. Honda:** None. **H. Matsuzaki:** None. **T. Kishimoto:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.03/ZZ7

Topic: G.07. Other Psychiatric Disorders

Support: Natural Sciences and Engineering Research Council of Canada

Title: An image reconstruction approach to characterizing the topography of emotional face space related to borderline personality disorder

Authors: *C.-H. CHANG[1], A. C. RUOCCO[1], N. DROBOTENKO[1], A. C. LEE[1,2], A. NESTOR[1]
[1]Dept. of Psychology at Scarborough, Univ. of Toronto, Toronto, ON, Canada; [2]Rotman Res. Institute, Baycrest Ctr., Toronto, ON, Canada

Abstract: Difficulties in recognizing facial emotional expressions may cause interpersonal problems, such as those observed in individuals with borderline personality disorder (BPD). Previous studies have suggested that individuals with BPD tend to be less accurate at recognizing emotions and sometimes misperceive emotions. However, prior work on emotion recognition in BPD has relied primarily on a small range of prototypical emotional expressions, limiting the generality of the conclusions from this research. It is also unclear how individuals with BPD misperceive facial expressions. Additionally, it is unknown whether individuals with BPD have similar biases in their memory of emotional expressions. The current work, therefore, aims to address these issues with the aid of an image reconstruction approach as applied to a relatively large set of facial expressions. Specifically, the goal of this approach is to reveal the pictorial information of visual representations associated, in the current context, with perception and memory for facial expressions. To this end, participants with BPD and healthy controls provided similarity ratings of emotional expressions for pairs of visually-presented face stimuli or for pairs

consisting of one face stimulus and a face recalled from memory. These ratings were then used to construct a multidimensional facial expression space for each individual. Subsequently, the appearance of faces viewed or recalled from memory, were reconstructed separately for each participant through a combination of significant features and dimensions derived from the facial expression space. Our findings establish the feasibility of reconstructing images of facial expressions from perception and memory data. Reconstruction results provide evidence for differences in the structure of expression representations for individuals with BPD compared to healthy controls. Further, we evaluate the reconstruction accuracy of different expressions and we establish the differential sensitivity to negative bias across a range of emotional expressions. In summary, the present work provides a novel approach to examing the representation of facial expressions from perception and memory in healthy adults and in individuals with BPD.

Disclosures: C. Chang: None. **A.C. Ruocco:** None. **N. Drobotenko:** None. **A.C. Lee:** None. **A. Nestor:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.04/ZZ8

Topic: G.07. Other Psychiatric Disorders

Support: Conacyt CB221453 to MA

Title: Interleukin 6 involvement in a rodent model of chronic fatigue syndrome

Authors: *R. D. CUEVAS OLGUIN[1], T. MARES-BARBOSA[1], R. VELÁZQUEZ-CONTRERAS[1], M. MIRANDA-MORALES[2], S. ROSE-JOHN[3], M. ATZORI[4]
[1]UASLP, San Luis Potosi, Mexico; [2]Facultad de Ciencias, Univ. Autonoma De San Luis Potosi, San Luis Potosi, Mexico; [3]Christian Universitet, Kiel, Germany; [4]Univ. Autónoma de San Luis Potosí, San Luis Potosi, Mexico

Abstract: Chronic fatigue syndrome (CFS) is a disorder characterized by extreme fatigue unexplained by any underlying medical condition. CFS does not improve with rest, but can worsen with physical or mental activity. Since infection and immune challenge are possible triggers for CFS, a role for cytokines has been hypothesized in the etiology of CFS. The pro-inflammatory cytokine interleukin 6 (IL-6) has been positively correlated to the onset of numerous stress-triggered neuropsychiatric conditions including schizophrenia, depression, anxiety, and autism. We wondered whether IL-6 is involved in the expression of CFS. To answer this question, we compared the behavior of a group of wild type animals (WT), with that of genetically modified mice in which IL-6 central trans-signaling was blocked by overexpression of the IL-6 transducer glycoprotein 130 by the promoter of the astrocytic marker glial fibrillary

acidic protein (GFAP-sgp130Fc, TG). C57BL/6 mice where submitted to a protocol of 3 injections of Brucellla abortus (BA), one every 2 weeks during 6 weeks, as model for CFS. Motor activity was monitored during the whole duration of the experiment in four groups: saline- or BA-injected WT, and saline- or BA-injected TG. Motor activity was measured with an automated system allowing to monitor the number of turns of a spinning wheel and other motor parameters for individually lodged mice continuously during the whole duration of the experiment. Our results show that BA (vs. saline) injections significantly reduce motor activity (90 ± 14% vs. 44 ± 7%, n = 11, 10, respectively) in WT, but not in TG animals (82 ± 20% vs. 63 ± 7%, n = 10 each). Porsolt forced swimming, sucrose preference, and elevated plus-maze tests suggest that both WT and TG BA-injected animals display increased depression, anhedonia, and anxiety, while gripping strength was unaltered by BA-injections in all groups. Our data corroborate the hypothesis that central IL-6 trans-signaling is a critical factor in the induction of CFS.

Disclosures: R.D. Cuevas Olguin: None. **T. Mares-Barbosa:** None. **R. Velázquez-Contreras:** None. **M. Miranda-Morales:** None. **S. Rose-John:** None. **M. Atzori:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.05/ZZ9

Topic: G.07. Other Psychiatric Disorders

Support: National Science Center grant no OPUS 2015/17/B/NZ7/02984 (J.Wierońska)

Title: The interaction between muscarinic and mGlu2/3 in animal models of schizophrenia

Authors: *J. M. WIERONSKA[1], P. CIEŚLIK[2], M. WOŹNIAK[2], A. PILC[3]
[1]Dept. of Neurobiology, Inst. of Pharmacol., Krakow, Poland; [2]Inst. of Pharmacol. PAS, Krakow, Poland; [3]Inst. of Pharmacol., 31-343 Krakow, Poland

Abstract: The role of $GABA_B$ receptor in the antipsychotic-like action of mGlu4 receptor orthosteric agonist LSP4-2022.
Variety of our previous research showed that the action of the ligands of metabotropic receptors for glutamate is dependent on the others neurotransmitters in the central nervous system. We also showed that synergistic action between mGlu4 and muscarinic M4 receptors may be proposed as alternative therapy for schizophrenia. Here, we assessed the mutual action of M4 and mGlu2/3 receptors ligands in selected animal models of schizophrenia. DOI-induced head twitches test in mice, social interaction test in rats and novel object recognition test. VU152100 was used as positive allosteric modulator of M4 receptors and LY487379 was used as positive allosteric modulator of mGlu2/3 receptors. Both compounds induced clear and dose-dependent

antipsychotic-like action in all three tests at the doses 0.5, 1 and 3 mg/kg (LY487379) or 0.25, 0.5, 1, 2 and 5 mg/kg (VU152100). Our results show that the simultaneous administration of both compounds in subeffective doses induced clear antipsychotic-like effect similar to that observed for each active dose alone. The combinations did not disturbed motor coordination of animals when measure in rotarod test. Therefore, the antipsychotic treatment based on the activation of both mgLu2/3 and M4 receptors could be proposed as an alternative therapy to presently used neuroleptics.
The study was supported by National Science Center grant no OPUS 2015/17/B/NZ7/02984 (J.M. Wierońska)

Disclosures: J.M. Wieronska: None. **P. Cieślik:** None. **M. Woźniak:** None. **A. Pilc:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.06/ZZ10

Topic: G.07. Other Psychiatric Disorders

Support: R01MH113858

Title: The impact of cortical interneurons on synaptic development in neuropsychiatric disorders

Authors: *A. KATHURIA[1], R. KARMACHARYA[2]
[1]Harvard Med. Sch., Boston, MA; [2]Harvard Univ., Boston, MA

Abstract: Schizophrenia (SCZD) is a crippling neurological disorder with a world-wide prevalence of 1%. Cognitive impairments is the most important predictor of functional outcomes in patients with schizophrenia. However, efficacious treatment of cognitive deficits in psychotic disorders remains a significant challenge in clinical practice. Even though, antipsychotic medications provide symptom relief by reducing hallucinations, they do not improve the cognitive deficits that is the core feature in schizophrenia. There is an urgent need for new therapeutic approaches that target the neurobiology of cognitive impairments. Our research focuses on developing stem cell-based models to study the molecular and cellular basis of schizophrenia using iPSCs (Induced pluripotent stem cells) generated from patients. We are investigating the functional connection between excitatory and inhibitory cortical neurons derived from patient and healthy iPSCs. Currently, we have identified decrease in synaptic co-localisation and spine density in the patient lines. Therefore, focusing our research on high-throughput screens of small molecule libraries to discover compounds that can normalize/modulate cellular disease signatures.

Disclosures: A. Kathuria: None. **R. Karmacharya:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.07/ZZ11

Topic: G.07. Other Psychiatric Disorders

Support: NARSAD 25242

Title: Induction of hippocampal hyperactivity by dentate gyrus inhibition

Authors: *D. SCOTT[1], C. A. TAMMINGA[2]
[1]Psychiatry, UT Southwestern, Dallas, TX; [2]Univ. of Texas Southwestern Med. Ctr. at Dallas, Dallas, TX

Abstract: Although psychosis is the defining and the most recognizable symptom domain in schizophrenia, the biological mechanisms underlying psychosis remains unknown. Analysis of post-mortem human hippocampal tissue and in vivo human imaging studies in schizophrenia have detected abnormalities within hippocampal subfields: decreased GluN1 within the dentate gyrus (DG), along with increased synaptic plasticity markers in CA3 and increased *in vivo* basal activity within CA3/CA1 which correlates with psychosis severity. We have previously demonstrated in a mouse model that CA3 hyperactivity per se is sufficient to induce psychosis-like behaviors in mice. However, the mechanism underlying the induction of this hippocampal hyperactivity remains unclear. Recent work suggests that decreased excitatory drive onto CA3 pyramidal cells from the mossy fiber results in homeostatic upregulation of CA3 activity. We hypothesize that decreasing DG granule cell activity in mice would result in a replication of both the brain pathology associated with psychosis, i.e., increased basal activity and synaptic markers in CA3, and a psychosis-like behavioral phenotype. To address this, we infused male C57BL6/J mice (n >6/group) with AAVs containing either DREADDs or a control virus to specifically inhibit DG granule cells, allowing manipulation of activity with spatial, temporal, and cell-type specificity. Following surgery, we chronically treated mice with clozopine-N-oxide, assessed basal activity in the hippocampal subfields through expression of cFos, measured synaptic markers with Western blotting, and performed behavioral analysis, utilizing paradigms associated with a psychosis-like phenotype in mice: prepulse inhibition, fear conditioning, and social memory. Scientific rigor was ensured by repeating each experiment in multiple cohorts of mice, and analyses were performed using automated methodology when possible, to eliminate experimental bias. Results suggest that decreasing DG activity does result in hippocampal hyperactivity, and the magnitude of this resultant hyperactivity determines the presence of a psychosis-like behavioral phenotype. Experiments to determine levels of synaptic proteins are still underway.

Disclosures: D. Scott: None. **C.A. Tamminga:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.08/ZZ12

Topic: G.07. Other Psychiatric Disorders

Support: ADA post doctoral fellowship

Title: SK_3 KO in 5-HT neurons inhibits binge-like eating in mice

Authors: *Y. HE, X. CAI, P. XU, Y. YANG, C. WANG, H. LIU, I. HYSENI, Y. XU, 77030 Baylor Col. of Med., Houston, TX

Abstract: Neural networks that regulate binge eating remain to be illustrated, and effective treatments for binge eating are limited. Our previous data showed that local inhibition of a small conductance Ca^{2+}-activated K^+ (SK) current in the dorsal Raphe nuclei (DRN) markedly suppressed binge-like eating in female mice through the ER-alpha receptor mediates signal pathway. Here we first combined qPCR and immunohistochemistry to establish that SK3 highly expressed in serotonin (5-HT) neurons in the DRN while other two isoforms of SK channel are not expressed. Further we use genetic engineering techniques to specific knock out (KO) SK3 in DRN area in mouse brains. We demonstrated that after SK3 was KO in 5-HT neurons resulted in spontaneous action potential (AP) firing frequency increase and depolarization of the resting membrane potential (RP) in 5-HT neurons. These suggest that loss of SK3 in in 5-HT neurons will increase the neuronal activity. Further study in binge like eating behavior we found that mice with SK3 KO in 5-HT neurons showed reduced binge like eating compare to the WT control mice without change the anxiety behavior. I.C.V injection of SK3 selective blocker apamin suppress binge-like eating behavior in WT mice while not in SK3 KO mice. Thus, we identified the SK3 in 5-HT neurons as one potential target for anti-binge therapies.

Disclosures: Y. He: None. **X. Cai:** None. **P. Xu:** None. **Y. Yang:** None. **C. Wang:** None. **H. Liu:** None. **I. Hyseni:** None. **Y. Xu:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.09/ZZ13

Topic: G.07. Other Psychiatric Disorders

Title: Autonomic imbalance in women with premenstrual syndrome: A model disease of allostatic load

Authors: Y. MENG[1], *R. ZHOU, SR[2]
[2]Dept. of Psychology, [1]Nanjing Univ., Nanjing, China

Abstract: Introduction Allostatic load occur while individuals are undergoing stressors frequently, have poor reaction and delayed recovery of related physiological responses. This is embodied in the dysregulation of autonomic nervous system (ANS) and hormone secretion. It is unclear whether the Premenstrual Syndrome (PMS) is caused by an allostatic load of premenstrual stress. The purpose of this study is explore whether or not the ANS of PMS female has a dull response and a delayed recovery to the stress.
Method By measuring heart rate variability (HRV, sympathetic and parasympathetic response of ANS) of PMS group(n=50) and health group(n=46), this study aimed to evaluate the response and recovery of the ANS and the related emotional experiences after stress during the menstrual cycle. The Biopac MP150 was been used to measure the HRV at rest and their changes during stress tasks (speech task and mental arithmetic task) and recovery phase. The emotional experience were measured before and after the tasks.
Results In the resting state, the sympathetic response (LF/HF) of the participants during the luteal phase was higher than that of the follicular phase ($F_{(1, 94)}$=40.22, p<0.05, ηp2=0.30), and the PMS was significantly lower than the healthy ($F_{(1, 94)}$=7.76, p<0.05, ηp2=0.076). The parasympathetic response (HF) does not change significantly throughout the process (p>0.05). During the stress tasks, the LF/HF results of the two groups was presented in Figure 1. The negative emotional experience of the PMS individuals during the luteal phase was significantly increased (p<0.05).
Conclusion No matter at rest or stress tasks, PMS group had a duller sympathetic response than healthy group during luteal phase, and they also had slow recovery time after tasks, which illustrated PMS women have autonomic imbalance during the premenstrual period. The autonomic imbalance also increases individual's negative feelings to stress. The function of the ANS was discussed starting from the theory of allostatic load, which helps to explain the mechanism of PMS and the causes of negative emotions.

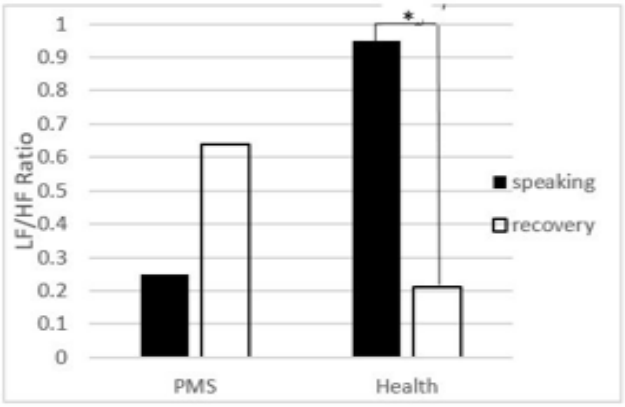


Fig 1. A. The change effect in LF/HF ratio in the speaking and recovery periods for two groups.

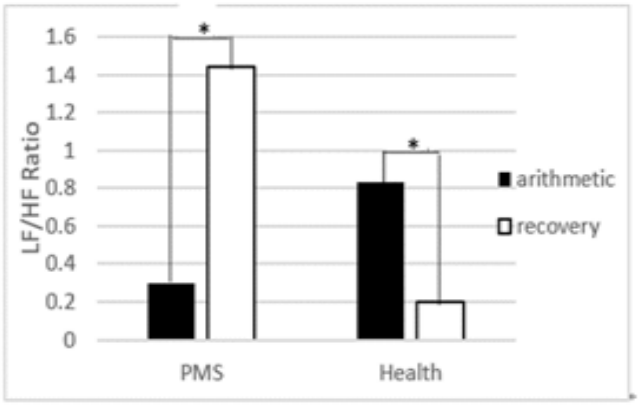


Fig 1. B. The change effect in LF/HF ratio in the arithmetic and recovery periods for two groups.

Disclosures: Y. Meng: None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.10/ZZ14

Topic: G.07. Other Psychiatric Disorders

Title: Anticipation of negative stimuli lead to blunted activation of negative emotion in females with premenstrual syndrome

Authors: *L. CHEN[1], R. ZHOU, SR[2,3]
[1]Dept. of Psychology, Nanjing Univ., Jiangsu Province, China; [2]Dept. of Psychology, Nanjing Univ., Nanjing, China; [3]Ctr. for Exptl. Social and Behavioral Res. of Jiangsu Province, Nanjing, China

Abstract: Introduction Premenstrual syndrome(PMS) consists of regularly recurring psychological or somatic symptoms, or both; the symptoms occur specifically during the luteal phase of the cycle and are relieved by the onset of, or during, menstruation(Yonkers, K. A., O'Brien, P. S., & Eriksson, E,2008). Patients with PMS had significantly enhanced reactivity during anticipation of negative emotional stimuli(Bannbers et al. ,2011;Gingnell et al.,2013). For healthy people, anticipatory emotion didn't influence emotion processing if they can make effortful anticipatory cognitive distraction(Erk, Abler, & Walter (2006). However, anticipation of negative stimuli attenuated emotion processing for the depression patients(Rosenblau et al, 2012).So this research aims to study if the anticipation will affect the subsequent emotion processing of PMS females. **Methods** 42 female university students were divided into two groups by scores of the Chinese Premenstrual Syndrome Scale: PMS group (n=22), and non-PMS group (n=21). There is significant difference between their scores for this scale ($t_{(41)}$=14.644, p<0.001), no difference in age, length of menstrual cycle and length of menstrual flow. The participates were asked to watch positive or negative emotion pictures(IAPS) after the clue of the green or the red patch, and they also watched the same pictures after no clues in the luteal phase and follicular phase while the ERPs were recorded. **Results** The mean amplitudes of P300 from 350-500ms at PZ were analyzed by a three-way mixed ANOVAs: 2 (group: PMS, non-PMS) × 2 (condition: positive pictures with clue, negative pictures with clue, positive pictures without clue, negative pictures without clue) ×2(menstrual phase: luteal phase, follicular phase). The results showed that the main effect of condition was significant ($F_{(3,39)}$= 24.87, p=0.029, η^2=0.657) and the interaction between the group and condition was significant ($F_{(3,39)}$= 3.342, p=0.029, η^2=0.204)while the other interactions were not significant. For the PMS group, the P300 of the negative pictures without the clue were significantly greater than these with the clue(p=0.004), but there were no remarkable differences between these two conditions in non-

PMS group (p=1.000). For non-PMS group, the P300 of the negative pictures with clue were larger than that of positive pictures with clue(p=0.014) while PMS females didn't have significant differences between these two conditions(p=0.097). **Conclusion** Compared with non-PMS female, anticipation of negative stimuli lead to blunted activation of negative emotion in PMS females and this blunted activation is not related to the menstrual phase.

Disclosures: L. Chen: None. **R. Zhou:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.11/ZZ15

Topic: G.07. Other Psychiatric Disorders

Support: Rutgers University Chancellor's Seed Grant

Title: Investigating the neurobehavioral mechanisms of motivational control in Attention Deficit/Hyperactivity Disorder

Authors: *A. O. CECELI[1], J. Y. NATSHEH[2], D. CRUZ[3], E. TRICOMI[1]
[1]Psychology Dept., Rutgers Univ. - Newark, Newark, NJ; [2]Kessler Fndn., East Hanover, NJ; [3]Counseling Services, Rutgers Univ., Newark, NJ

Abstract: Attention Deficit/Hyperactive Disorder (ADHD) is characterized by pronounced distractibility and impulsivity. Additionally, reward processing deficits and paralleling aberrance in the brain's reward circuitry have been reported, suggesting sub-optimal decision-making. The neurobehavioral mechanisms of motivational control in ADHD remain elusive. Motivational control of action is governed by a balance between caudate- and prefrontal cortex-regulated goal-directed actions that are executed in pursuit of desirable outcomes, and posterior putamen-regulated habits that are outcome-insensitive. We tested whether ADHD is associated with an over-reliance on habitual control and posterior putamen hyperactivity. Twenty-three patients and 23 matched controls were trained on a free-operant reward-learning task while undergoing fMRI. Participants learned two novel stimulus—response—outcome associations where instrumental responses to fractal cues predicted either M&M or Goldfish outcomes in variable-interval reinforcement. After moderate training, we removed subjects from the MRI scanner and devalued one of the two snacks via selective satiety. A subsequent extinction task in the scanner tested whether subjects performed outcome-driven, goal-directed behaviors (i.e., diminished response rate to fractal predicting devalued snack), or cue-driven, habitual actions (i.e., persistent response rate towards devalued snack). Despite behavioral similarities between patient and control groups, ROI analyses suggest posterior putamen hyperactivity in ADHD patients. Furthermore, whole-brain analyses reveal a shift from anterior to posterior putamen recruitment

over training in ADHD. These findings highlight the potential role of striatal sub-regions in strengthening novel associations in ADHD. Further research directed towards understanding the motivational and neural underpinnings of ADHD may be imperative in developing biomarkers for improved diagnostic and interventive methods.

Disclosures: A.O. Ceceli: None. **J.Y. Natsheh:** None. **D. Cruz:** None. **E. Tricomi:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.13/ZZ17

Topic: G.07. Other Psychiatric Disorders

Support: NIH grant AA022448

Title: Significant interaction between purinergic P2X4 receptors and dopamine D1 receptors in mediation of prepulse inhibition of acoustic startle reflex and underlying molecular mechanisms

Authors: *S. KHOJA[1], L. ASATRYAN[2], M. W. JAKOWEC[3], D. L. DAVIES[2]
[2]Titus Family Dept. of Clin. Pharm., [3]Dept. of Neurol., [1]USC, Los Angeles, CA

Abstract: Ivermectin (IVM), a dihydro lactone derivative obtained from the soil actinomycete, *Streptomyces avermitilis*, is a FDA-approved drug for treatment of parasitic infections. Mechanistically, IVM acts as an allosteric positive modulator of purinergic P2X4 receptors (P2X4Rs) that are ion channels gated by adenosine-5'-triphosphate (ATP). Recently, we found that IVM induced deficits in prepulse inhibition (PPI), enhanced thigmotactic behavior and increased levodopa-induced motor behavior in male C57BL/6J mice. We were interested in IVM's effects on PPI, since IVM induced PPI dysfunction and this effect was attenuated in P2X4R knockout (KO) mice, implicating a role for P2X4Rs in this behavior. PPI deficits are often associated with cognitive impairments and are linked to a wide spectrum of neurological disorders. Interestingly, the PPI deficits in P2X4R KO mice were rescued by dopamine (DA) receptor antagonists indicating an interaction between P2X4Rs and DA receptors in PPI regulation. On the basis of findings from P2X4R KO mouse model, we hypothesized that modulation of DA receptors can alter the effects of IVM on PPI. This was accomplished by testing the effects of DA D1 and D2 receptor antagonists, SCH 23390 (1mg/kg) and raclopride (3 mg/kg) respectively and D1 agonist, SKF 82958 (0.1mg/kg) in regulation of IVM-mediated effects on PPI. To elucidate the mechanisms by which dopaminergic drugs modulate IVM-mediated PPI deficits, we investigated the interaction between IVM and dopaminergic drugs on phosphorylation of signaling molecules linked to PPI regulation including dopamine and cyclic-AMP regulated phosphoprotein of 32kDa (DARPP-32), Ca^{2+}/calmodulin kinase IIα (CaMKIIα) and neuronal nitric oxide synthase (nNOS) in the ventral striatum, a critical region for PPI

regulation. We found that SCH 23390, but not raclopride, significantly attenuated the PPI disruptive effects of IVM. Furthermore, SKF 82958 tended to potentiate IVM-mediated PPI disruption. At the molecular level, SCH 23390 and raclopride significantly blocked IVM-mediated increase in DARPP-32 phosphorylation in the ventral striatum, whereas SKF 82958 significantly potentiated IVM's effects on DARPP-32 phosphorylation in the same brain region. Additionally, SCH 23390 blocked IVM-mediated effects on CaMKIIα phosphorylation, but there was no interaction between IVM and raclopride or SKF 82958 in regulation of this enzyme. Overall, these findings suggest an involvement for D1 receptors in IVM-mediated PPI disruption via modulation of DARPP-32 and CamKIIα phosphorylation, indicating a complex interaction between P2X4Rs and D1 receptors on PPI and underlying signaling pathways.

Disclosures: S. Khoja: None. **L. Asatryan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Liana Asatryan is an inventor on a patent for the use of ivermectin for treatment of alcohol use disorders. **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 L. Davies is an inventor on a patent for the use of ivermectin for treatment of alcohol use disorders.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.14/ZZ18

Topic: G.07. Other Psychiatric Disorders

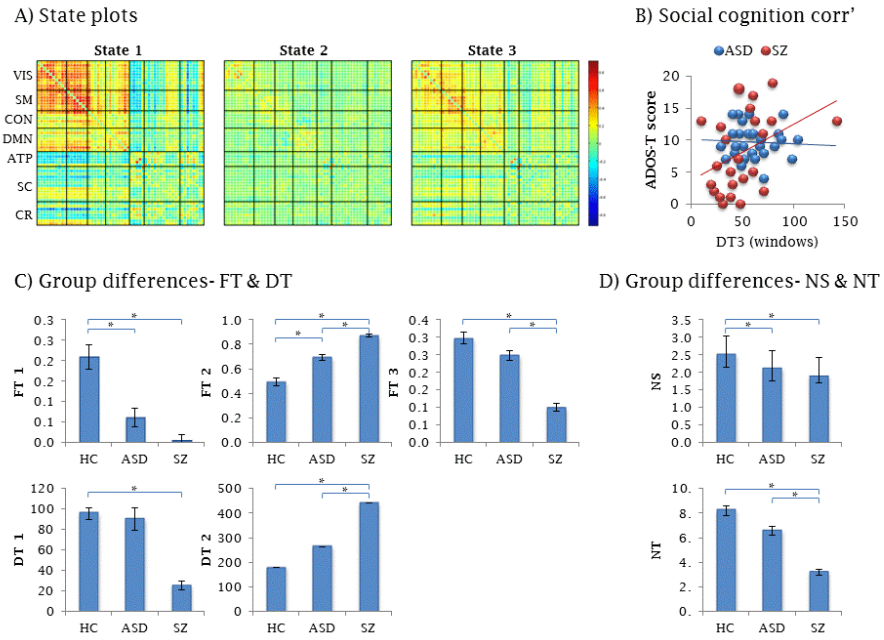
Support: NIMH: R01 MH095888

Title: Temporal dynamics in schizophrenia and autism spectrum disorder: Convergence, divergence and classification

Authors: *L. RABANY[1], S. BROCKE[2], V. CALHOUN[3], B. PITTMAN[4], S. CORBERA[5], B. E. WEXLER[4], M. D. BELL[4], K. A. PELPHREY[6], G. D. PEARLSON[2,4], M. ASSAF[7,4]
[1]Olin Neuropsychiatry Res. Ctr., Inst. of Living, Hartford, CT; [2]Olin Neuropsychiatry Res. Center, Inst. of Living, Hartford, CT; [3]The Mind Res. Network, Albuquerque, NM; [4]Yale University, Sch. of Medicine, Dept. of Psychiatry, New Haven, CT; [5]Central Connecticut State University, Dept. of Psychological Sci., New Britain, CT; [6]Autism & Neurodevelopmental Disorders Inst., George Washington Univ., Virginia Beach, VA; [7]Olin Neuropsychiatry Res. Center, Inst. of, Hartford, CT

Abstract: Background: Over the recent years there has been a growing debate regarding the extent and nature of the overlap in neuropathology between schizophrenia (SZ) and autism

spectrum disorder (ASD). Dynamic functional network connectivity (dFNC) is a recent analysis method that explores temporal patterns of functional connectivity (FC). We compared resting-state dFNC in SZ, ASD and matched healthy controls (HC), characterized the association between temporal connectivity and behavior, and preformed classification analysis based on dFNC parameters. **Methods:** Resting-state fMRI was collected from 100 individuals: 33 SZ, 33 ASD, 34 HC. High-order independent component analysis (ICA) was performed, followed by dFNC analysis (window=30s, step=1TR, k-means clustering) using the GIFT toolbox. Number of transitions (NT), number of states (NS), fraction time (FT), and dwell time (DT) were calculated per subject. These measures were compared between groups using ANOVA, correlated with symptoms, and entered into linear discriminant analysis (LDA). **Results:** Three re-occurring FC states were identified (Fig A): 1. cortico-cortical, 2. weak, intra-network, 3. strong cortico-cortical. *Both clinical groups* (Fig C,D) showed decreased NS [P=0.001] and increased $FT_{state\text{-}2}$ and decreased $FT_{state\text{-}1}$ [P<0.001]. *The SZ group* further showed decreased NT [P<0.001] and $FT_{state\text{-}3}$ [P<0.001], and increased $DT_{state\text{-}2}$ [P<0.001] compared to HC and ASD, and decreased $DT_{state\text{-}1}$ [P=0.001] compared to HC. $DT_{state\text{-}3}$ correlated with social functioning score (ADOS; Fig B) in SZ [P=0.043; r=0.416]), but not ASD. Classification results correctly identified SZ at high rates (specificity- 81.8%), while ASD and HC were correctly classified at low rates (50%, 41%; respectively). **Conclusions:** Results indicate a severe and pervasive pattern of temporal aberrations in SZ (specifically, being "stuck" in a state of weak connectivity), that distinguishes SZ participants from both ASD and HC, and is uniquely associated with social functioning.



Disclosures: L. Rabany: None. **S. Brocke:** None. **V. Calhoun:** None. **B. Pittman:** None. **S. Corbera:** None. **B.E. Wexler:** None. **M.D. Bell:** None. **K.A. Pelphrey:** None. **G.D. Pearlson:** None. **M. Assaf:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.15/ZZ19

Topic: G.07. Other Psychiatric Disorders

Support: Brain Research Program 2013M3C7A1056101
Bio & Medical Technology Development Program 2016M3A9D5A01952412
Mid-Career Researcher Program 2017R1A2B4008875
Science Research Center 2015R1A5A1009024

Title: Exploration of novel dopaminergic circuitry regulating impulsivity

Authors: *B. KIM[1], S. YOON[1], R. NAKAJIMA[2], Y.-K. LEE[1], J.-S. CHOI[1], B.-J. YOON[1], G. AUGUSTINE[3], J.-H. BAIK[1]
[1]Korea Univ., Seoul, Korea, Republic of; [2]Ctr. for Functional Connectomics, Korea Inst. of Sci. and Technol., Seongbukgu, Seoul, Korea, Republic of; [3]Nanyang Technological Univ., Singapore, Singapore

Abstract: Dopamine is broadly implicated in important brain functions such as motor control, cognition, memory, motivation and reward. Dopamine D2 receptor (D2R) plays crucial roles for such dopaminergic functions. It has been reported that polymorphism of dopamine D2 receptor genes can lead to drug addiction associated with impulsivity, schizophrenia and attention deficit/hyperactivity disorder (ADHD). Using 5-choice serial reaction time task (5-CSRTT), we measured attention and impulsivity in wild type (WT) and D2R knockout (D2R -/-) mice. D2R -/- mice showed significantly lower accuracy and higher premature response than WT mice. Selective optogenetic activation of D2R expressing neurons via microinjection of channelrhodopsin (AAV-DIO-hChR2(H134R)-eYFP) into the central amygdala (CeA) of D2R-Cre mice induced a decrease of premature response. Further, we identified synaptic connectivity from D2R-expressing neurons of CeA to bed nucleus of the stria terminalis (BNST) via ChR2-assisted circuit mapping. Selective optogenetic activation of D2R-expressing neurons in CeA-BNST circuit caused a decrease of impulsivity. These studies revealed a novel dopaminergic circuit that plays a crucial role in impulsive behavior which is important component of reward-related psychiatric disorders.

Disclosures: B. Kim: None. **S. Yoon:** None. **R. Nakajima:** None. **Y. Lee:** None. **J. Choi:** None. **B. Yoon:** None. **G. Augustine:** None. **J. Baik:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.16/ZZ20

Topic: G.07. Other Psychiatric Disorders

Support: NARSAD Young Investigator Award
NIMH K01MH096175-01
OCAST Grant HR10-141
William K. Warren Foundation

Title: Changes in fMRI BOLD signal pre- and post- weight restoration in subjects treated for anorexia nervosa: Implications for the use of neuroimaging in eating disorders research

Authors: *D. DEVILLE[1], K. L. KERR[2], S. MOSEMAN[3], J. BODURKA[4], W. K. SIMMONS[5]
[1]Laureate Inst. for Brain Res., Tulsa, OK; [2]Human Develop. and Family Sci., Oklahoma State Univ., Tulsa, OK; [3]Laureate Psychiatric Clin. and Hosp., Tulsa, OK; [4]Stephenson Sch. of Biomed. Engingeering, Univ. of Oklahoma, Norman, OK; [5]Mood Disorders Biomarkers, Jannsen Res. & Develop., San Diego, CA

Abstract: Anorexia nervosa (AN) has been linked to functional and structural brain differences, and functional MRI has been increasingly utilized to examine the neurobiological processes underlying AN. However, indiscriminate use of BOLD imaging in underweight AN patient samples may pose methodological concerns due to physiological effects of malnutrition on the brain. While several studies have drawn conclusions about the psychological features of AN from fMRI research using patients who are significantly underweight, to date there is no published research on the reliability of the BOLD signal in acutely ill AN patients. We therefore sought to examine BOLD signal strength in response to a visual checkerboard task in AN patients over the course of weight restoration. Prior research demonstrates strong test-retest reliability and reproducibility of activation within occipital and posterior thalamic regions in response to the checkerboard task.
Fifteen right-handed female subjects (mean age = 16.1 years, SD = 2.32, range = 13-20 years) undergoing inpatient treatment for AN participated in the current study and completed fMRI scanning at two time-points: at the beginning of treatment (mean body mass index [BMI]= 15.8 kg/m^2, SD = 1.5, range = 12.6-17.6), and after weight restoration (mean BMI = 19.5 kg/m^2, SD = 0.6, range = 18.7-20.5). Subjects were unmedicated at both time points. During fMRI scanning, subjects viewed a flashing black and white checkerboard alternating with a fixation screen. The checkerboard and control blocks were presented 12 times each, lasting for 17.5 seconds at a time. We used a dependent t-test to compare task-related BOLD activation from each time point (i.e., pre- and post- weight restoration) and found that following weight restoration, subjects exhibited

significantly decreased activation in occipital and thalamic regions. Further, the magnitude of reduction in BOLD signal strength in these regions from pre- to post- weight restoration was significantly correlated with AN patients' underweight BMI, such that a lower BMI was associated with a greater change in BOLD signal strength (r = -0.51 and r = -0.43 for occipital and thalamic clusters respectively) from the first to second time-point. These findings suggest that investigators should be mindful when including underweight subjects in fMRI research, and that results of studies that include underweight individuals should be interpreted cautiously. The effects of significantly low body weight on the BOLD signal may be accounted for by several different factors related to the malnourished state, and future research should aim to elucidate these specific mechanisms.

Disclosures: D. Deville: None. **K.L. Kerr:** None. **S. Moseman:** None. **J. Bodurka:** None. **W.K. Simmons:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.17/ZZ21

Topic: G.07. Other Psychiatric Disorders

Support: Division of Intramural Research of NINR

Title: Cognitive impacts of fatigue induced in a mouse model of radiation therapy

Authors: B. S. WOLFF[1], L. R. FENG[1], *K. FUKUHARA[3], L. SALIGAN[2]
[1]Natl. Inst. of Nursing Res., [2]NINR/IR, NIH, Bethesda, MD; [3]Intramural Res., Natl. Inst. of Nursing Res., Bethesda, MD

Abstract: Fatigue is a common and distressing symptom following radiation therapy for cancer, and it can be frequently undertreated in clinical practice. It is commonly defined as a subjective feeling of exhaustion that is not alleviated by rest or sleep, and it is likely a symptom with very complex underlying biology. It is strongly associated with other symptoms, including cognitive deficits. To explore the relationship between fatigue and cognitive symptoms, we use our previously established mouse model of radiation-induced fatigue, in which mice developed fatigue-like behavior after receiving radiation targeted to a region in their lower abdomen. In this study, we compared the fatigue-like behavior measured by home cage running wheel activity with cognitive performance in the Y-maze, 0-maze, and open field tests in irradiated mice vs sham-irradiated controls. In separate experiments, we also compared fatigue-like behavior measured by spontaneous home cage ambulatory activity with cognitive performance in a home cage learning task in irradiated mice vs sham-irradiated controls. We found that peripheral irradiation, despite not targeting the central nervous system, reduces cognitive performance in

the Y-maze test and may have complex effects on behavior in the open field and 0-maze tests. These results support the idea that fatigue and cognitive symptoms can have similar biological origins, and animal models may help develop treatments targeted either to particular symptoms or to a broader symptom cluster.

Disclosures: B.S. Wolff: None. **L.R. Feng:** None. **K. Fukuhara:** None. **L. Saligan:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.18/ZZ22

Topic: G.07. Other Psychiatric Disorders

Support: NIH Grant MH057440

Title: Normalization of VTA dopamine neuron activity activity by mGluR2/3 agonist pomaglumetad methionil in the methylazoxymethanol acetate model of schizophrenia

Authors: *S. SONNENSCHEIN[1], A. A. GRACE[2]
[1]Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [2]Univ. of Pittsburgh Dept. of Neurosci., Pittsburgh, PA

Abstract: Pomaglumetad methionil, a group 2 metabotropic glutamate receptor (mGluR2/3) agonist, showed promise as a novel antipsychotic in preclinical research but failed to show efficacy in clinical trials, though it has been suggested that it may be effective in certain patient populations. Although previous studies have shown that mGluR2/3 agonists have no effect on dopamine (DA) in normal rats, we used the methylzoxymethanol acetate (MAM) rat model of schizophrenia to determine whether pomaglumetad may regulate DA neuron activity in a model representative of the hyperdopaminergic state thought to underlie psychosis, compared to control (SAL) rats. MAM and SAL rats were treated with pomaglumetad methionil (1, 3, 10 mg/kg, i.p) or 1 mg/kg saline 30 minutes prior to anesthetized in vivo electrophysiological recordings. The population activity of VTA DA neurons was measured by passing an electrode in a grid-like pattern, counting the number of spontaneously firing DA neurons, and analyzing their firing rate and bursting activity. Pomaglumetad dose-dependently reduced the number of spontaneously active DA neurons in the VTA of MAM rats to control levels without affecting DA firing in SAL rats. In rats treated with 3mg/kg pomaglumetad for 14d, DA neuron activity remained reduced in MAM rats, without effect in SAL rats, suggesting lack of tolerance following repeated daily treatment. As in the MAM rats, DA neuron population activity can be increased in a hippocampal-dependent manner via acute restraint stress. Administration of 3 mg/kg pomaglumetad prior to 2h restraint stress prevented the restraint-induced increase in DA neuron activity, and this effect was blocked by pretreatment with an mGluR2/3 antagonist. Thus, the

ability of pomaglumetad methionil to reduce the hyperdopaminergic activity in both MAM rats and in normal rats following restraint stress suggests that it can indirectly regulate DA neuron activity, likely by reducing increased ventral hippocampal activity, which may contribute to its potential therapeutic effects.

Disclosures: S. Sonnenschein: None. **A.A. Grace:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.19/ZZ23

Topic: G.07. Other Psychiatric Disorders

Support: FAPESP
CNPq
IBRO

Title: Titration-based BDNF dual effect underlies the opposed behavioral effect of CB1 and TRPV1 agonists

Authors: *C. A. DINIZ[1], C. BIOJONE[2], S. R. L. JOCA[3], E. CASTRÉN[2], F. S. GUIMARÃES[1], P. C. CASAROTTO[2]
[1]Pharmachology, Sch. of Med. of Ribeirão Preto - Univ., Ribeirao Preto, Brazil; [2]Neurosci. Center, Univ. of Helsinki, Helsinki, Finland; [3]Sch. of Pharmaceut. Sci. - Univ. of São Paulo, Ribeirão Preto, Brazil

Abstract: Rationale: anandamide (AEA) or 2-arachidonoylglycerol (2AG), both CB1 agonists, induce CB1 coupling to transactivate TRKB (*Tropomyosin receptor kinase B),* thus regulating the neuronal migration and maturation in the developing cortex. However, at higher concentrations AEA also engages vanilloid receptor - TRPV1, usually with opposed consequences on behavior, especially concerning anxiety. Then, the aim of the present study was to investigate the interaction between CB1/TRPV1 and TRKB systems in a mouse model of anxiety/repetitive behavior, along with *in vitro* approach. **Methods:** male C57BL67j were used to behavioral protocols and cortex of E18 rat embryos were dissected and cultured. Marble burying test (box with 5cm sawdust layer and twelve marbles evenly spaced over the floor) was used to evaluate repetitive behavior. Mice were placed on box´s center and 25min later the number of buried marbles was counted. Western blotting or ELISA were used to quantify protein levels and stereotaxic surgery to cannulate the animals. **Results:** systemic infusion of WIN (CB1 agonist, 1mg/kg) decreased the number of buried marbles, while previous K252a (TRK blocker, 80ug/kg) treatment prevented it. Infusion into prefrontal cortex of AEA (o.5pmol) and ACEA (more selective CB1 agonist, 0.05pmol) decreased, while capsaicine (CPS, TRPV agonist;

5pmol) and BDNF (endogenous TRKB agonist, 200pg) increased the number of buried marbles ($F(3,32)= 11.74$). About *In vitro* results, treatment with AEA 100 and 200nM ($F(5,18)= 16.53$), CPS 200nM ($F(3,19)= 9.28$) and BDNF 20 and 50ng/ml ($F(3,16)= 134.40$) increased pTRK levels. AEA 100nM ($F(1,20)= 16.01$), but not BDNF 20ng/ml ($F(1,16)= 0.85$), increased pTRK levels by activating CB1 receptor. With a previous capsazepine (TRPV1 antagonist) 20uM treatment, the excess of pTRK levels guaranteed with AEA 200nM treatment was reversed to the same levels obtained with AEA 100nM ($F(2,30)= 17.04$). Previous treatment with TRKB.fc (BDNF scavenger) also brought the effect of AEA 200nM to the levels of pTRK found with AEA 100nM treatment ($F(2,18)= 15.01$). AEA 200nM increased pTRK levels by increasing BDNF levels released in the medium, since levels of pTRK and BDNF were positively correlated (Spearman's $r= 0.77$). Accordingly, capsaicine 200nM increased pTRK levels, effect which was also prevented with previous TRKB.fc treatment ($F(1,20)= 9.28$). All the data were considered significant with $p<0.05$. **Conclusion:** our data suggest a complex interaction between CB1, TRPV1 and TRKB, whose final balance modulates burying behavior. The amount of BDNF released might mean an additional modulatory mechanism by which CB1 and TRPV1 display opposite effects**.**

Disclosures: C.A. Diniz: None. **C. Biojone:** None. **S.R.L. Joca:** None. **E. Castrén:** None. **F.S. Guimarães:** None. **P.C. Casarotto:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.20/ZZ24

Topic: G.07. Other Psychiatric Disorders

Support: Wheaton College G.W. Aldeen Memorial Fund

Title: Effects of chronic exercise training on fatigue: A meta-analysis & meta-regression analysis

Authors: *S. CHEN[1], N. THOM[2], M. P. HERRING[3], D. C. MONROE[4]
[1]Univ. of California-Los Angeles, Los Angeles, CA; [2]Biol., Wheaton Col., Wheaton, IL; [3]Physical Educ. and Sport Sci., Univ. of Limerick, Limerick, Ireland; [4]Neurol., UC Irvine, Irvine, CA

Abstract: Objectives: The neurobiological mechanisms of fatigue are poorly understood. And though it is a public health burden there are few effective, evidence-based treatment options. Studies suggest that exercise training reduces symptoms of fatigue, but the evidence from RCTs on the effect of exercise training on fatigue has not been synthesized since 2006. This study estimated the population effect size for exercise training effects on fatigue, and determined to

what extent participant and trial characteristics moderated these effects, in order to guide work seeking to uncover the neurobiological mechanisms of fatigue.
Methods: One hundred eighty-six effects were derived from 109 articles comprised of 12,470 participants (mean age = 52.37±15.01 y, 75% female/25% male). Studies included both randomization to exercise training (n = 6,355) or non-active control (n = 6,115), and a validated fatigue outcome measured at baseline and post-intervention. Hedges' *d* effect sizes were computed, and random effects models were used for analyses. Meta-regression quantified the extent to which participant and trial characteristics moderated the mean effect.
Results: Exercise training significantly reduced feelings of fatigue by a heterogeneous mean effect size delta (Δ) of 0.49 ($z=10.74$, $p<.0001$, 95CI:[0.40, 0.58], $Q_{T[182]}=987.07$, $p<.001$).
The overall meta-regression model was significant ($Q_{R7}=26.40$, $p=.0004$, $R^2=.14$; $Q_{E103}=168.25$, $p<0.001$). Sex (B=.32, z=2.84, p=.005), disease status (B=.32, z=2.24, p=.03), and intervention length (B=.33, z=3.33, p=.0009), accounted for significant variation in the overall effect of exercise on fatigue. However, age (B=-.01, z=-.10, p=.92), exercise mode (B=.22, z=1.47, p=.14), exercise intensity (B=-.06, z=-.45, p=.65), and exercise time (B=.34, z=1.52, p=.13) were not related to effect size.
Larger effects were found among men (Δ=1.06, 95CI: .40, 1.71), those with cancer or a fatigue-related disease (Δ=.62, 95CI: .48, .75), and for exercise interventions < 12 weeks (Δ=.97, 95CI: .72, 1.23).
Conclusion: The results suggest that exercise training produces moderate reductions in fatigue and that translational investigations designed to explain the neurobiological mechanisms of exercise can optimize fatigue reduction by employing programs of <12 weeks among those with cancer or fatigue-related diseases. It may be advised to allow individuals to choose exercise mode, intensity, and time in order to promote compliance as these factors did not moderate fatigue reductions. More research in young adults (< 40y) is warranted given the comorbidity of fatigue with other psychosomatic disorders that are rising in the population.

Disclosures: S. Chen: None. **N. Thom:** None. **M.P. Herring:** None. **D.C. Monroe:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.21/ZZ25

Topic: G.07. Other Psychiatric Disorders

Support: U19MH82441
R01DA045657
RO1MH112205

Title: Beta-arrestin2 is required for the behavioral responses to lysergic acid diethylamide

Authors: *W. C. WETSEL[1], R. M. RODRIGUIZ[1], V. M. POGORELOV[1], V. NADKARNI[1], J. D. MCCORVY[2], B. L. ROTH[3]
[1]Dept Psychiat & Behav Sci., Duke Univ. Med. Ctr., Durham, NC; [2]Dept Cell Biology, Neurobio. & Anat., Med. Col. Wisconsin, Milwaukee, WI; [3]Dept Pharmacol., Univ. of North Carolina Chapel Hill Med. Sch., Milwaukee, WI

Abstract: Drugs stabilize specific G protein-coupled receptors (GPCRs) conformations essential for canonical G protein- and β-arrestin- (βArr) mediated signaling. Preferential signaling through G protein-dependent or -independent pathways has been termed functional selectivity, whereby agonists can stabilize distinct signaling complexes referred to as biased agonism (for review see Wacker et al., *Cell* 2017). Recently, we have developed an Arr-biased D2 agonist (UNC9994) that displays potent antipsychotic-like activity *in vivo* (Allen et al., *PNAS* 2011; Park et al., *Neuropsychopharmacology* 2016). Importantly we showed that the behavioral effects of UNC9994 require βArr2 by comparing effects in wild-type (WT) and βArr2 knockout (KO) mice. Lysergic acid diethylamide (LSD) is a potent agonist for most serotonin (5-hydroxytryptamine; 5-HT) receptors (Wacker et al., *Science* 2013) and many other biogenic amine receptors (Kroeze et al., *Nature Struct and Mol Biol* 2015). At 5-HT_2-family receptors, however, LSD is a potent Arr-biased agonist (Wacker et al., *Cell* 2017) and in humans the psychedelic effects of LSD have been ascribed primarily to 5-HT_{2A} receptor agonism. Here, we sought to determine if the behavioral actions of the hallucinogen LSD also require βArr2 in mice. Accordingly, we examined whether mice with global deletion of *Arrb2* respond differently to LSD than WT controls. Adult WT and βArr2-KO mice (N≈10 mice/group) received vehicle or LSD (i.p.) and were evaluated in tests for open field activity, prepulse inhibition (PPI), and ethological behaviors. Baseline motor activities in the open field were similar for WT and βArr2-KO mice. LSD stimulated locomotor activity, rearing, and stereotypical activities in WT mice while these behaviors were blunted in βArr2-KO mutants. The 5-HT_{2A} antagonist MDL-100907 reduced the LSD-stimulated locomotion and rearing in both genotypes; stereotypy was unaffected with the antagonist only in mutants. LSD suppressed PPI in WT, whereas it was unaffected in βArr2-KO mice; MDL-100907 rescued WT responses. LSD increased head-twitch, grooming, and retrograde walking to greater extents in WT than mutant mice, while MDL-100907 decreased these responses. Nose-pokes were enhanced in WT, but not in βArr2-KO mice; MDL-100907 normalized WT responses. Collectively, many LSD-mediated responses are reduced or abrogated when *Arrb2* is disrupted in mice. These findings are consistent with the hypothesis that βArr2-modulated signaling may be critical for LSD's behavioral effects.

Disclosures: W.C. Wetsel: None. **R.M. Rodriguiz:** None. **V.M. Pogorelov:** None. **V. Nadkarni:** None. **J.D. McCorvy:** None. **B.L. Roth:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.22/ZZ26

Topic: G.07. Other Psychiatric Disorders

Support: NARSAD Grant

Title: Overexpression of dopamine D2 receptors on ventral striatal indirect pathway neurons reduces survival in the activity-based anorexia paradigm

Authors: *A. C. WELCH[1], M. S. MCMURRAY[2], S. C. DULAWA[1]
[1]Psychiatry, Univ. of California San Diego, La Jolla, CA; [2]Psychology, Miami Univ., Oxford, OH

Abstract: Anorexia nervosa (AN) is an eating disorder characterized by severe hypophagia and weight loss, and an intense fear of weight gain. In the activity-based anorexia (ABA) paradigm, rodents exposed to running wheels and restricted food access exhibit extreme weight loss, hypophagia, and hyperactivity compared to rodents exposed to only one of these conditions. Upon reaching 75% of their initial bodyweight, mice are removed from the experiment. Days of survival in the ABA paradigm provide a measure of ABA susceptibility. Thus, the ABA paradigm provides a model for aspects of AN. We previously reported that chronic treatment with dopamine D2 receptor (D2R), D3R, or D2/D3R antagonists reduce weight loss and hypophagia, and increase survival in the ABA paradigm. Furthermore, human imaging studies have reported that recovered female AN patients show increased D2/D3R binding in the ventral striatum. However, whether D2/D3R overexpression in the ventral striatum plays a causal role in AN remains unexplored. We determined the effects of virally overexpressing D2Rs on ventral striatal indirect pathway neurons on ABA in mice. Eight week old transgenic male and female Drd2-cre mice received infusions of an adenoassociated virus (AAV) separately expressing the long form of D2R and mVenus in a Cre-dependent fashion, or a control virus expressing only EGFP in a Cre-dependent fashion. Thus, D2Rs were not ectopically expressed on striatal direct pathway neurons. Four weeks later, mice were 12 weeks old and tested in the open field paradigm, followed 2 days later by the ABA paradigm. Mice were placed in the open field chamber for 30 minutes and movement recorded. Our results showed increased locomotor activity in mice overexpressing D2Rs ($P < .0001$). Mice were then singly housed with a running wheel and received food and water ad lib during baseline. Dependent measures were collected daily for 4 days: bodyweight, food consumption, and wheel running distance. After the baseline period, food was available 7 hours each day starting one hour into the light period (12h:12h). During the restriction phase, the same measures were collected daily, and days of survival were also recorded. The restriction phase lasted up to 14 days. Our results showed that mice

overexpressing D2Rs in ventral striatal indirect pathway neurons showed reduced survival in the ABA paradigm (P <.05) compared to controls. This effect was observed in female (P <.05), but not male mice. Our findings suggest that overexpression of D2Rs on ventral striatal indirect pathway neurons increase ABA behavior and may play a causal role in the development of AN.

Disclosures: A.C. Welch: None. **M.S. McMurray:** None. **S.C. Dulawa:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.23/AAA1

Topic: G.07. Other Psychiatric Disorders

Title: Decreased empathy and functional network alteration in a mice model of ostracism

Authors: *S. JUNG[1], J.-H. YOON[2], J. CHUNG[2], Y. JEONG[3]
[1]Korea Advanced Inst. of Sci. and Technol., Taejon-City, Korea, Republic of; [3]Bio and Brain Engin., [2]KAIST, Daejeon, Korea, Republic of

Abstract: Formation and maintenance of social bonding are critical to survival of social animals. Being ignored, rejected and excluded, called ostracism, could break the bonding and threat the quality of life of individuals. Though ostracism is common in any social groups, the effects and the underlying mechanisms are largely unknown. Various paradigms such as social isolation, and social defeat have been developed to understand the effects of being ostracized especially in rodents, however, the existing paradigms are insufficient to explain ostracism because of individualized housing. Here, we developed social exclusion paradigm by make mice carrying butyric acid, smelly liquid making other mice avoid. The social exclusion mouse (SEM) model repeatedly experienced being avoided, staying alone, and being groomed less by cage-mates (allogrooming). SEM showed impaired sociability and empathy-like behaviors chronically. After empathy-like behavior test, *c-fos* driven functional network analysis revealed increased functional connectivity in basolateral amygdala (BLA) connectivity, while in dentate gyrus in control mice. Furthermore, SEM used more segregated network modules than control mice. In conclusion, our repeated social exclusion paradigm could induce the ostracism-like effects and lead to impaired social behaviors and change functional connectivity networks. It may contribute to understand the effects of social exclusion and underlying neural mechanisms.

Disclosures: S. Jung: None. **J. Yoon:** None. **J. Chung:** None. **Y. Jeong:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.24/AAA2

Topic: G.07. Other Psychiatric Disorders

Support: Brain Canada
NSERC
CIHR
ERANET
INSERM
CNRS
ANR

Title: Role of striatal cholinergic interneurons in the regulation of dopaminergic neurotransmission and implication for striatal-dependent processes

Authors: *M. FAVIER[1,2], H. JANICKOVA[3], M. A. PRADO[3], V. F. PRADO[3], S. EL MESTIKAWY[4]
[1]Psychiatry, Douglas Mental Hlth. Univ. Inst., Montréal, QC, Canada; [2]McGill Univ., Montréal, QC, Canada; [3]Robarts Res. Institute/University of Western Ontario, London, ON, Canada; [4]Psychiatry, Douglas Mental Hlth. Univ. Institute/McGill Univ., Montréal, QC, Canada

Abstract: Cholinergic interneurons (ChIs) from the dorsal striatum are major regulators of striatal function. ChIs express the vesicular acetylcholine transporter (VAChT) but also the atypical vesicular glutamate transporter type 3 (VGLUT3), and consequently signal using both acetylcholine (ACh) and glutamate (Glu). Our study is focused on deciphering the role of Ach/Glu cotransmission by ChIs in the regulation of dopaminergic (DA) neurotransmission and striatal-dependent processes. Using genetic and virus-targeted approaches to delete the expression of VAChT or VGLUT3 in mice, we discovered that ChIs finely modulate DA neurotransmission, by using ACh and Glu which have opposite effects on DA release. Further, we demonstrated that this DA regulation by ChIs was differential across the ventral and dorsal parts of the striatum. We will investigate the functional consequences of this ChIs-driven regulation of DA release using specific behavioural tasks known to assess for striatal-dependent processes.

Disclosures: M. Favier: None. **H. Janickova:** None. **M.A. Prado:** None. **V.F. Prado:** None. **S. El Mestikawy:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.25/AAA3

Topic: G.07. Other Psychiatric Disorders

Support: CRC-15-04-KIST
NRF-2017R1A2B2003993
2015R1D1A1A01058556

Title: Cocaine drives schizophrenia-like behaviors via cholinergic neurons within ventral striatum

Authors: *S. HAM, H.-I. IM
Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: The function of cocaine as a dopamine reuptake inhibitor plays an important role in establishing and maintaining addiction. However, when used heavily, more than half of cocaine users showed behaviors similar to schizophrenia: it is usually called as cocaine-induced psychosis (CIP) that include hallucinations, delusions, delirium, suicidal thoughts, and loss of touch with reality. Despite seriousness of the disorder, however, very little is known about the neurological mechanisms that mediate CIP. On the other hand, the involvement of various neurotransmitters in psychotic behaviors of schizophrenia had generated considerable interest, which was how cocaine's pharmacological and molecular interactions might affect behavioral changes via neurotransmitter systems. Here, we successfully established CIP mouse model. Subsequently, by examining changes of neurotransmitters in several brain regions, we have found that the level of dopamine and acetylcholine have increased in ventral striatum. Interestingly, the dopaminergic neurons in ventral tegmental area and substantia nigra showed any changes in CIP mice compared to control, whereas the cholinergic neurons in ventral striatum were significantly reduced in CIP mice than in control. Furthermore, schizophrenia-like behaviors of the CIP mice were significantly rescued by nicotine and donepezil (acetylcholinesterase inhibitor). These findings suggest that part of schizophrenia-like behaviors induced by cocaine may be mediated via dysfunction of cholinergic neurons within ventral striatum.

Disclosures: S. Ham: None. **H. Im:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.26/AAA4

Topic: G.07. Other Psychiatric Disorders

Title: Regulation of amygdalar corticotropin releasing hormone in the peripartum period

Authors: *S. ZOUBOVSKY[1], J. SCHULKIN[2], L. MUGLIA[3]
[1]Univ. of Cincinnati, Cincinnati, OH; [2]Dept. of Neurosci., Georgetown Univ., San Rafael, CA; [3]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

Abstract: Postpartum depression (PPD) affects 10-20% of women and exerts adverse consequences on mother and child. Fluctuations in estrogen (E2) and progesterone (P4) during pregnancy and transition to postpartum period are thought to be important in mediating functional alterations in the maternal brain needed for the emergence of maternal behaviors. However, E2 and P4 changes are also thought to be involved in PPD. Gestational stress and hypothalamic-pituitary-adrenal (HPA) axis abnormalities have also been implicated in the development of PPD. Here, we measure effects of perinatal changes in E2-P4 on corticotropin-releasing hormone (CRH), a principal modulator of the HPA axis and behavioral stress response, and on nuclear steroid hormone receptors/co-chaperones associated with CRH regulation. C57Bl/6 female mice have a significant increase in CRH mRNA in the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST) in the early postpartum period compared to virgin controls. This change is associated with a significant increase in CeA and BNST progesterone receptor (PR) mRNA, although no changes in glucocorticoid receptor (GR) expression are observed. Furthermore, there is a significant upregulation in mRNA of co-chaperones known to orchestrate GR/PR transcriptional activity. Increased CeA PPID and FKBP5 and BNST PPID, FKBP4, and BAG1 expression are observed in the early postpartum period suggesting these molecules as putative regulators of postpartum changes in GR/PR signaling. To further understand if the increase in CeA CRH is mediated by perinatal changes in E2-P4, we measured changes in CRH in an exogeneous E2-P4 model that mimics hormonal levels seen in the peripartum period. There is a significant increase in CeA CRH mRNA following E2-P4 withdrawal when compared to oil withdrawal controls. These changes are associated with behavioral alterations including a significant decrease in latency to first open arm entry in the elevated zero maze and a significant increase in immobility episodes in the forced swim test, suggesting an increased state of alertness. While perhaps beneficial for maternal behavior, this can also create an affective state vulnerable to environmental insults, such as chronic stress. These results provide evidence of postpartum alterations in GR/PR signaling in CeA-BNST neural circuitry following E2-P4 withdrawal. The mechanistic role GR/PR play in mediating CRH changes as well as the effects of gestational stress on GR/PR signaling and their

contribution to postpartum affective dysregulation are currently being investigated by selective spatiotemporal GR/PR modulation using Cre-loxP technology.

Disclosures: S. Zoubovsky: None. **J. Schulkin:** None. **L. Muglia:** None.

Poster

683. Other Psychiatric Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 683.27/AAA5

Topic: G.07. Other Psychiatric Disorders

Support: NIH Grant MH103366-01A1

Title: Neural white matter distinctions in biologically classified psychosis

Authors: *C. R. BURTON[1], B. S. JACKSON[2], L.-Y. HUANG[1], D. A. PARKER[2], D. J. SCHAEFFER[4], E. S. GERSHON[5], M. S. KESHAVAN[6], G. D. PEARLSON[7], C. A. TAMMINGA[8], B. A. CLEMENTZ[3], J. E. MCDOWELL[3]
[1]Neurosci., [2]Psychology, [3]Psychology, Neurosci., Univ. of Georgia, Athens, GA; [4]Robarts Res. Inst., Western Univ., London, ON, Canada; [5]Psychiatry and Behavioral Neuroscience, Human Genet., Univ. of Chicago, Chicago, IL; [6]Psychiatry, Harvard Med. School, Beth Israel Deaconess Med. Ctr., Boston, MA; [7]Psychiatry, Neurobio., Yale Univ. Sch. of Medicine, Olin Neuropsychiatry Res. Center, Inst. of Living/Hartford Hosp., Hartford, CT; [8]Psychiatry, Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Psychotic disorders share common phenomenology and genetic risk factors, but specific etiologies and targeted pharmacological treatments remain elusive. Schizophrenia (SZ), schizoaffective disorder (SZA), and bipolar disorder with psychosis (BPP) are all diagnosed based on clinical symptoms, which in their lack of diagnostic specificity, evidence homogeneity between disorders historically considered distinct. Separating probands based on neurobiology instead may yield more meaningful classifications which offer better targets for study of disease mechanisms and treatments. The Bipolar and Schizophrenia Network for Intermediate Phenotypes consortium has collected brain and behavioral data from probands with these three disorders and used k-means clustering and multivariate discriminant analysis to regroup probands into three “Biotypes” based on electrophysiological, oculomotor, and cognitive measures. The present study examines measures of neural white matter (WM), which were not included in the original Biotypes analysis, in order to determine whether Biotypes provide better group separation than diagnostic classification. Diffusion-weighted imaging data were acquired from probands with SZ (n=76), SZA (n=74), and BPP (n=14), as well as healthy comparison (HC) subjects (n=76); fractional anisotropy (FA) values indexing WM structure were calculated and compared between the three diagnostic groups, as well as between the three Biotypes

previously derived. Between diagnoses, mean FA was lower for SZ and SZA probands than HC across several WM tracts connecting frontal, temporal, parietal, and posterior regions, but often not different between BPP probands and HC. Between Biotypes, mean FA was lower for Biotype 1, which includes probands from all three diagnostic categories, than for HC or the other Biotypes across similar tracts. WM differences between Biotypes may reflect true biological alterations, which ultimately provide better classification and possible targets for etiological mechanisms and treatments in psychosis.

Disclosures: C.R. Burton: None. **B.S. Jackson:** None. **L. Huang:** None. **D.A. Parker:** None. **D.J. Schaeffer:** None. **E.S. Gershon:** None. **M.S. Keshavan:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Sunovion, GlaxoSmithKline. **G.D. Pearlson:** None. **C.A. Tamminga:** F. Consulting Fees (e.g., advisory boards); Intra-Cellular Therapies, Inc.. Other; Eli Lilly, Sunovion, Astellas, Pfizer, Merck, National Alliance on Mental Illness, American Psychiatric Association, Autifony, The Brain and Behavior Foundation, National Academy of Medicine. **B.A. Clementz:** None. **J.E. McDowell:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.01/AAA6

Topic: G.07. Other Psychiatric Disorders

Support: Macalester College

Title: Grooming displays robust face validity in the neonatal clomipramine exposure rat model of obsessive compulsive disorder

Authors: *L. PEEBLES[1], K. HILBER[1], J. BICE[1], Z. BUSBY[1], W. FRYLING[1], M. STELZNER[1], D. S. KREISS[1,2]
[1]Macalester Col., Saint Paul, MN; [2]Freshman Res. Immersion Program, Binghamton Univ., Binghamton, NY

Abstract: Obsessive Compulsive Disorder (OCD) is a chronic neuropsychiatric illness that affects 2-3% of the United States population and is characterized by persistent anxiety producing thoughts accompanied by overwhelming urges to perform repetitive ritualistic 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. Animal models of this psychiatric disorder offer an invaluable tool whereby new therapeutic avenues can be explored. Although multiple behavioral assays have been suggested to reflect the repetitive and compulsive symptoms of OCD, no single behavior has been universally accepted as a model of the disorder.

The objective of this study was to explore grooming as an alternative to other types of anxiety-related behaviors in the assessment of the OCD-like phenotype in a novel animal model of OCD induced by neonatal exposure to clomipramine, a serotonin/norepinephrine reuptake inhibitor. Prior studies have demonstrated that the neoclomipramine rodent model has both face and predictive validity in the Hole Board (HB) and Elevated Plus Maze (EPM). In the current study, for the first time, grooming was selected for analysis in this novel model given its frequent over-expression in OCD patients. Grooming, rearing, and HB behaviors were repeated assessed over 3 trials (separated by 1-2 weeks) in adult male Sprague-Dawley rats that had been injected neonatally (Day 9-16) with either 15 mg/kg clomipramine (neoCLOM, n=20) or with saline (neoSAL, n=20). Neo-CLOM "OCD-like" rats consistently exhibited increased grooming versus neo-SALINE control rats across all 3 Trials ($*p_1 = 0.049$, $**p_2 = 0.0071$, $**p_3 = 0.0037$). In contrast, no significant differences between the experimental groups were observed for rearing or head poking measures. Likewise, analysis of the rats' behaviors in the EPM showed no significant differences between these two groups of rats and data from the multiple trials had considerable variability. In conclusion, this study demonstrates that an analysis of grooming offers valuable advantages over other anxiety-related measures as a behavioral assay for animal models of OCD. Grooming behaviors robustly demonstrate phenotypic differences between experimental "OCD-like" and control rats, is consistently expressed across trials, and has high face validity with the human disorder.

Disclosures: L. Peebles: None. **K. Hilber:** None. **J. Bice:** None. **Z. Busby:** None. **W. Fryling:** None. **M. Stelzner:** None. **D.S. Kreiss:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.02/AAA7

Topic: G.07. Other Psychiatric Disorders

Support: Macalester College

Title: Overcoming the one trial tolerance of rat behavior in the elevated plus maze (EPM)

Authors: *K. M. HILBER[1], C. BRANTNER[1], E. CARTER[1], W. FRYLING[1], F. LI[1], S. MOCHIDA[1], H. MUDRICK[1], K. NAZAROVA[1], M. STELZNER[1], D. S. KREISS[1,2]
[1]Macalester Col., Saint Paul, MN; [2]Neurosci. Stream, Freshman Res. Immersion Program, Binghamton Univ., Binghamton, NY

Abstract: Rodent models of anxiety disorders often employ the Elevated Plus Maze (EPM). A higher ratio of time spent in the CLOSED versus OPEN arms of the maze is associated with a higher level of anxiety. A major limitation in using the EPM, however, is the "One Trial

Tolerance" phenomena (File, Mabbutt, & Hitchcott, 1990). This refers to dramatic drop in the animals' exploration of the OPEN arms following the initial exposure to the maze. It has thus been suggested that repeated testing in the EPM for a single rodent is thus experimentally invalid. The aim of this study was to investigate whether manipulation of selected variables of the experimental protocol could increase OPEN arm exploration of male Sprague-Dawley rats (n=20) upon repeated exposure to the arena. For the current study, rats were initially exposed to the arena at an early age (30 days postnatal), observational trials were separated by 10 days, the animals were frequently handled, the housing environments were enriched, and low illumination levels were used when assessing behavior. In accordance with prior studies, OPEN arm exploration was significantly decreased upon the 2nd exposure (Day 40) to the arena. However, by the 4th exposure (Day 60), OPEN arm activity was no longer different from the initial exposure. Moreover, by the 6th exposure (Day 80), OPEN arm activity was actually *increased* above that measured on the 1st Trial. This study thus demonstrates that procedural modifications of the experimental protocol can enable OPEN arm behavior to be fully restored upon successive exposures in the EPM - thereby overcoming the One Trial Tolerance limitation associated with this commonly used apparatus. Adopting these relatively minor experimental modifications enables the anxiety level of an individual rat to be assessed multiple times in the EPM - allowing for a repeated measures design and minimization of the number of animal subjects required for experimentation.

Disclosures: K.M. Hilber: None. **C. Brantner:** None. **E. Carter:** None. **W. Fryling:** None. **F. Li:** None. **S. Mochida:** None. **H. Mudrick:** None. **K. Nazarova:** None. **M. Stelzner:** None. **D.S. Kreiss:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.03/AAA8

Topic: G.07. Other Psychiatric Disorders

Support: PPP-125784
PP2-139101

Title: A novel negative allosteric modulator (NAM) of the cannabinoid receptor 1 (CB_1) as a potential therapeutic ligand for the treatment of psychiatric disorders arising from dopamine dysregulation

Authors: *V. LAM[1], G. BAILLIE[2], I. R. GREIG[3], M. H. ABDELRAHMAN[3], L. A. TREMBLEAU[3], R. A. ROSS[1]
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Univ. of Dundee, Nethergate, United Kingdom; [3]Univ. of Aberdeen, Aberdeen, United Kingdom

Abstract: The cannabinoid receptor 1 (CB_1) receptor is a G-protein coupled receptor (GPCR) that is ubiquitously expressed in the brain. It has been previously shown that CB_1 receptor antagonists have antipsychotic like effects in animal models of schizophrenia and has therefore been postulated that targeting the CB_1 receptor could provide a novel drug target for the treatment of several psychiatric diseases such as schizophrenia. Unfortunately, the side of effects of an orthosteric antagonist for the CB_1 receptor (rimonabant) in clinical trials led to the withdrawal of the drug from human use. The evidence is clear that the endocannabinoid system is an important and potential therapeutic target in psychiatry. With the discovery of an allosteric binding site on the CB_1 receptor it is possible that allosteric modulators of the CB_1 receptor may offer a unique and novel approach to rebalance the dopaminergic system at multiple points. By targeting the allosteric site of the CB1 receptor, we generated a novel negative allosteric modulator (NAM): ABM300. In cells stably expressing the CB_1 receptor, we assayed ABM300 in several orthogonal assays. These assays included arrestin recruitment, cAMP, and ERK phosphorylation. We tested the ability for ABM300 to allosterically modulate signalling of synthetic cannabinoids CP55940 and WIN55212. In our initial assays using arrestin recruitment, ABM300 was able to show negative allosteric modulation of the agonists CP55940. Further assessment using assays for quantifying cAMP signalling and ERK phosphorylation, also found that ABM300 was acting as a negative allosteric modulator. In addition, in vitro pharmacokinetic and toxicological analysis indicates that ABM300 is stable in our in vitro assays which predicts in vivo drug stability and penetrance into the central nervous system. In conclusion, we show that ABM300 is a novel negative allosteric modulator for the CB1 receptor. Based on its chemical properties, we expect ABM300 to be active in the central nervous system for further in vivo characterization.

Disclosures: V. Lam: None. **G. Baillie:** None. **I.R. Greig:** None. **M.H. Abdelrahman:** None. **L.A. Trembleau:** None. **R.A. Ross:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.04/AAA9

Topic: G.07. Other Psychiatric Disorders

Support: PPP-125784
PP2-139101

Title: Novel negative allosteric modulator (NAM) of Cannabinoid Receptor 1 (CB_1) ameliorates symptoms due to dopamine dysregulation in psychiatric disorders

Authors: *C. A. MIELNIK[1], I. R. GREIG[2], M. H. ABDELRAHMAN[3], L. A. TREMBLEAU[3], A. SALAHPOUR[1], A. J. RAMSEY[1], R. A. ROSS[1]

[1]Pharmacol. and Toxicology, Univ. of Toronto, Toronto, ON, Canada; [2]Inst. of Med. Sci., [3]Chem., Univ. of Aberdeen, Aberdeen, United Kingdom

Abstract: Background: The prevalence of psychiatric disorders is common, with anxiety, mood disorders, and schizophrenia reporting prevalence rates of 28.3%, 9.5%, and ~1% respectively. However, patient outcomes remain not ideal. Therefore, it is imperative to find novel treatment approaches for these disorders. Dopamine controls cognitive, emotional and motor aspects of goal-directed behaviour, with perturbations in the system playing a role in a number of psychiatric disorders and their underlying symptoms. Relating to the dopamine system, the endocannabinoid systems serves as an important filter of afferent inputs, helping shape how incoming information is conveyed onto dopamine neurons and to output targets. Therefore, we hypothesize that compounds negatively targeting the endocannabinoid system could be candidates in treating positive and affective symptoms in psychiatric illness. We tested the effect of ABM300, a novel negative allosteric modulator (NAM) of the CB_1 receptor (IC_{50} of ~20nM).
Methods: Adult (>P70) GluN1-knockdown (GluN1KD - F1: C57Bl/6J x 129S1/SvlmJ) and DAT-knockout (DATKO - C57Bl/6J), balanced for sex, were treated with either vehicle (1:1:18 – Tween80 : 95% ethanol : saline) or a novel CB_1 negative allosteric modulator (CB_1 NAM), ABM300, at 10mg/kg, tested on behavioural assays, and compared to littermate controls. Locomotor, stereotypic movements and vertical activity were tested, along with anxiety/mania and sensorimotor gating behaviours. All data were analyzed with two- or three-way ANOVA, as appropriate, and corrected for multiple comparisons.
Results: GluN1KD and DATKO mice display hyperactivity, impaired habituation and sensorimotor gating, along with increased stereotypy and vertical activity, in a state of mania-like behaviour. Following acute treatment with ABM300, amelioration of these dysregulated behaviours was observed. GluN1KD mice saw a reduction in locomotor and vertical activity, along with an amelioration of repetitive stereotypic movements and mania-like behaviour. DATKO mice also saw the same amelioration of behaviours as that of the GluN1KD, with additional amelioration of sensorimotor deficits.
Conclusion: The data suggest that CB_1 NAMs represent a novel treatment for psychiatric symptoms as a result of dopamine dysregulation. ABM300 ameliorates dopamine dysregulation in both animal models of psychiatric illness. Furthermore, targeting the endocannabinoid system offers the opportunity to normalize deficits that arise from differing underlying dysfunctions that manifest as similar behavioural changes; both of which are mediated by dopamine dysregulation.

Disclosures: C.A. Mielnik: None. **I.R. Greig:** None. **M.H. Abdelrahman:** None. **L.A. Trembleau:** None. **A. Salahpour:** None. **A.J. Ramsey:** None. **R.A. Ross:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.06/AAA11

Topic: G.07. Other Psychiatric Disorders

Title: SXC-2023, a potential therapeutic for various CNS disorders, is safe and well-tolerated in phase I clinical studies

Authors: *M. NEARY, C. E. BEYER, D. G. LAWTON, P. P. COTTER, T. BECK
Promentis Pharmaceuticals, INC, Milwaukee, WI

Abstract: A number of disorders of the central nervous system (CNS) are characterized by alterations in glutamatergic neurotransmission and/or oxidative homeostasis. Moreover, a robust impulsive behavioral phenotype and deficits in the brain's inhibitory control circuitry are key features of several of these chronic conditions. The cystine-glutamate antiporter (also known as System x_c^- or Sxc) is expressed within these inhibitory brain pathways (i.e., the cortico-striatal system), where it is capable of modulating glutamatergic signaling and increasing the synthesis of glutathione, an important antioxidant. SXC-2023, a small molecule activator of System x_c^-, is currently being developed for the treatment of trichotillomania, a neuropsychiatric impulse control disorder defined by recurrent hair pulling, which is accompanied by distress and other functional impairments. Here, we present the safety and tolerability profile of SXC-2023 from our first-in-human, Phase 1 studies in healthy volunteers. Following acute administration of a broad pharmacological dose range, SXC-2023 was shown to be safe and well-tolerated with no significant adverse events. Further human studies are underway to assess the safety and pharmacokinetic profile of SXC-2023 following repeated dosing in healthy volunteers. These clinical safety results, together with a compelling preclinical efficacy and toxicology profile (presented separately), suggest that SXC-2023 represents a safe, well-tolerated, and promising approach for the treatment of inhibitory/impulse control disorders such as trichotillomania.

Disclosures: **M. Neary:** A. Employment/Salary (full or part-time):; Employee of Promentis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock/stock option holder of Promentis Pharmaceuticals. **C.E. Beyer:** A. Employment/Salary (full or part-time):; Employee of Promentis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock/stock option holder of Promentis Pharmaceuticals. **D.G. Lawton:** A. Employment/Salary (full or part-time):; Employee of Promentis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock/stock option holder of Promentis Pharmaceuticals. **P.P. Cotter:** A. Employment/Salary (full or part-time):; Employee of Promentis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock/stock option holder of Promentis Pharmaceuticals. **T. Beck:** A. Employment/Salary (full or part-time):; Employee of Promentis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock/stock option holder of Promentis Pharmaceuticals.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.07/AAA12

Topic: G.07. Other Psychiatric Disorders

Support: the Swiss Contribution to the enlarged European Union (PSPB- 210/2010) to EK
the European Research Council Starting Grant (H715148) to EK

Title: Circuit- and symptom-specific targeted therapy of fragile X syndrome rescues cognitive impairments and normalizes synaptic plasticity in central amygdala

Authors: *E. A. KNAPSKA[1], A. PUSCIAN[2], M. WINIARSKI[1], J. BOROWSKA[1], S. LESKI[3], T. GORKIEWICZ[4], M. CHATURVEDI[1], J. CHMIELEWSKA[6], M. DZIEMBOWSKA[7], L. KACZMAREK[5]
[1]Nencki Inst. of Exptl. Biol. PAS, Warsaw, Poland; [2]Yale Sch. of Med., New Haven, CT; [3]Nencki Inst. of Exptl. Biol., Warszawa, Poland; [4]Neurophysiol., [5]Nencki Inst., Warsaw, Poland; [6]Ctr. of New Technologies, Univ. of Warsaw, Warsaw, Poland; [7]Ctr. of New Technologies, Univ. of Warsaw, Warszawa, Poland

Abstract: Fragile X Syndrome (FXS) resulting from the loss of Fragile X Mental Retardation Protein (FMRP) is the most common monogenetic cause of inherited mental disability and autism. FXS patients display a wide range of cognitive and social impairments, with very high phenotypic variability. However, targeted therapeutic approaches tailored to address particular FXS symptoms have not been developed yet. In both humans and mice lack of FMRP leads to elevated translation of matrix metalloproteinase-9 (MMP-9), an enzyme involved in activity-dependent reorganization of dendritic spines architecture. Notably, abnormal activity of MMP-9-dependent circuits specifically in central amygdala (CeA) disrupts reward learning. Here we show how brain-circuit specific approach aiming at particular molecular mechanism rescue behavioral deficits in symptom-specific manner. We injected Fmr1 knockouts (Fmr1 KO), a mouse model of FXS, with nanoparticles (NPs) releasing TIMP-1, an endogenous inhibitor of MMP-9, into the CeA and tested their cognitive and social abilities in the systems for automated behavioral phenotyping (IntelliCages and Eco-HAB). Further, we combined it with assessment of synaptic plasticity (long term potentiation, LTP) and high-resolution morphology of synapses (electron microscopy). We show that targeted, CeA-limited inhibition of hypertranslated MMP-9: (1) rescues cognitive but not social deficits, (2) normalizes severely impaired CeA LTP, and (3) reverses abnormal CeA synaptic morphology in Fmr1 KOs. NPs used for the delivery of the endogenous MMP-9 inhibitor gradually release the compound assuring stable therapeutic levels over several days. Presented results provide critical insights into molecular and neural correlates of FXS.

Disclosures: A. Puscian: None. **M. Winiarski:** None. **J. Borowska:** None. **S. Leski:** None. **T. Gorkiewicz:** None. **M. Chaturvedi:** None. **J. Chmielewska:** None. **M. Dziembowska:** None. **L. Kaczmarek:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.08/AAA13

Topic: G.07. Other Psychiatric Disorders

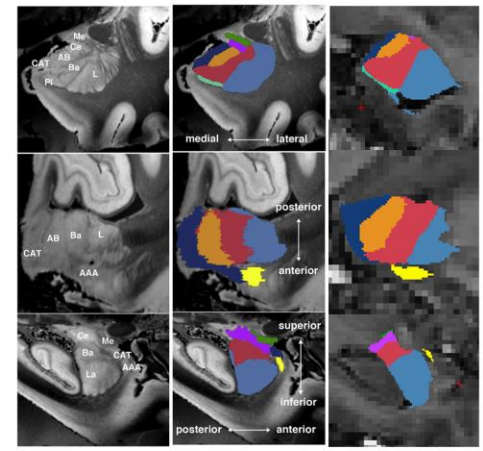
Support: NSFC 81671669

Title: Superficial but not basolateral amygdala volume decreases in medication-free patients with obsessive-compulsive disorder

Authors: L. ZHANG[1], X. HU[1], L. LU[2], X. HU[1], X. BU[1], H. LI[1], S. TANG[1], Y. GAO[1], Y. YANG[3], Q. GONG[1], *X.-Q. HUANG[2]
[1]West China Hosp. of Sichuan Univ., Chengdu, China; [2]West China Hosp. of Sichuan Univ., Sichuan, China; [3]Dept. of Psychiatry, West China Hosp. of Sichuan Univ., Chengdu, China

Abstract: Background:Abnormal activities of amygdala were frequently reported in patients with obsessive-compulsive disorder (OCD) but little is known about volumetric alterations in this small structure which consists of several functionally distinct nuclei. The current study aims to investigate the subfields volume in amygdala using a newly developed automatic segmentation technique[1] in a relatively large sample of medication-free OCD patients. **Methods:** High resolution 3D T1 weighted MR Imaging were collected from 81 OCD patients and 95 age- and sex-matched healthy controls(HC). Volume of whole amygdala and 9 subregions (anterior amygdaloid area, cortico-amygdaloid transition area; lateral nucleus, basal nucleus, paralaminar nucleus, accessory basal, medical nucleus, central nucleus and cortical nucleus) were measured using FreeSurfer 6.0. A MANCOVA with age, sex and ICV as covariates was performed to test for amygdala subregion volume differences between groups with Bonferroni correction and post hoc analysis was conducted to explore association between affected subregions and clinical profiles. **Results**: We found that OCD patients had reduced volume of bilateral amygdala (left, $p=0.034$; right, $p=0.002$) and subfields in superficial region including central nucleus(left, $p=0.002$; right, $p<0.001$), cortical nucleus(left, $p=0.001$; right, $p<0.001$) and medial nucleus(left, $p>0.05$; right, $p<0.001$) and in bilateral accessory basal nuclei (left, $p=0.001$; right, $p<0.001$), compared with HC. In addition, negative correlations were observed between illness duration and volume of right central nucleus ($p=0.022$, $r=-0.256$). **Conclusions**: We used a state-of-the-art amygdala segmentation approach and demonstrated that in patients with OCD, volumes reduction in the superficial amygdala regions were more

prominent relative to basal-lateral part and illness course had progressive effect on certain subregion. **Reference:** 1. NeuroImage, 2017,155:370-82



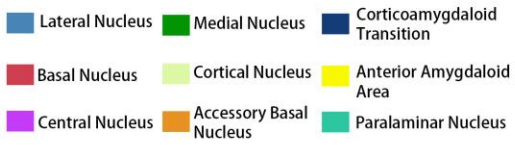
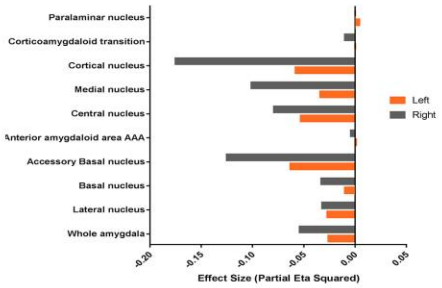
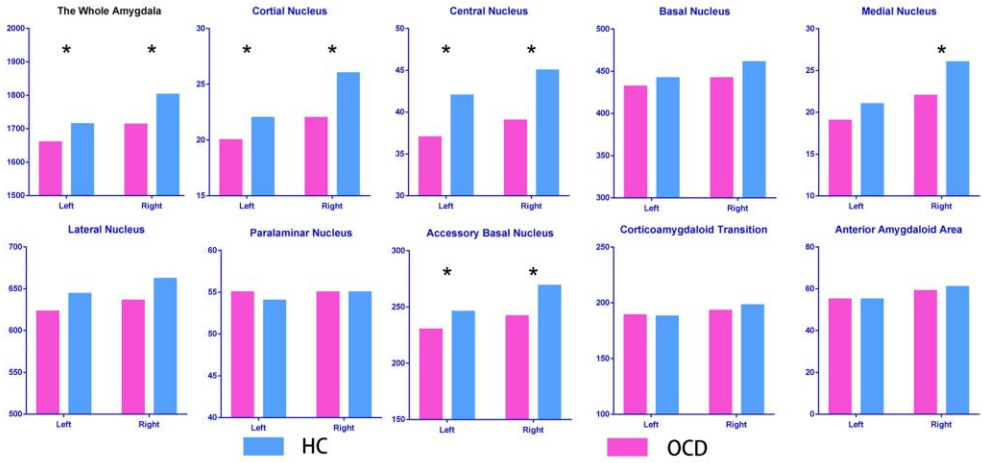


Table 1. Demographic and Clinical Data of Patients with Obsessive-Compulsive Disorder (OCD) and Healthy control (HC)

	OCD (n=81)	HC (n=95)	P value
Age, mean (SD), years	28.4 (8.0)	28.1(10.7)	0.836
Sex, n (% male)	50 (61.7)	59(62.1)	0.959
Education, mean (SD), years	14.1 (3.1)	NA	-
Illness duration, mean (SD), years	7.0 (5.1)	NA	-
YBOCS score, mean (SD)	21.9 (5.4)	NA	-
Obsession score, mean(SD)	13.2 (5.2)	NA	-
Compulsion score, mean(SD)	8.7 (5.3)	NA	-
HAMA score, mean(SD)	9.1 (3.7)	NA	-
HAMD score, mean(SD)	7.9(3.7)	NA	-

Notes: OCD: Obsessive-Compulsive Disorder. HC: Healthy Control. YBOCS: Yale-Brown Obsessive Compulsive Scale. HAMA: Hamilton Anxiety Scale. HAMD: Hamilton Depression Scale.





Disclosures: L. Zhang: None. **X. Hu:** None. **L. Lu:** None. **X. Hu:** None. **X. Bu:** None. **H. Li:** None. **S. Tang:** None. **Y. Gao:** None. **Y. Yang:** None. **Q. Gong:** None. **X. Huang:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.09/AAA14

Topic: G.07. Other Psychiatric Disorders

Support: NIH Grant DA005010
Shirley and Stefan Hatos Foundation

Title: Chronic pain upregulates kappa opioid receptor signaling in the amygdala

Authors: *A. L. SEVERINO[1,2], S. LIU[1,2], S. PICKENS[1,2], R. KARMOUTA[1,2], H. NASEF[1,2], F. M. LESLIE[3], F. I. CARROLL[4], C. J. EVANS[1,2], C. M. CAHILL[1,2]
[1]Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA; [2]Shirley and Stefan Hatos Fndn. Ctr. for Pharmacol., Los Angeles, CA; [3]Dept. of Pharmacol., UC Irvine, Irvine, CA; [4]Res. Triangle Inst., Research Triangle Park, NC

Abstract: Many patients with chronic pain also present with mood disorders such as anxiety or depression, which negatively impact their quality of life. Given the involvement of kappa opioid receptors (KOR) in eliciting aversive behaviors, including anxiety and depression, we asked whether KORs contribute to the negative affective-like behaviors commonly associated with chronic neuropathic pain. Kappa receptors are distributed widely throughout reward and emotion-processing circuitry including the amygdala, a brain region involved in emotional learning. Our study aimed to characterize KOR signaling-dependent negative affect in the chronic neuropathic (NP) pain state and determine whether KOR signaling is increased in the amygdala in the sciatic cuff model.

We induced NP pain in adult male and female C57/BL6 mice via cuff implantation around the left sciatic nerve or performed sham surgery without sciatic cuff as a control group. Mice developed typical mechanical and thermal allodynia as assessed with von Frey and cold plate tests by behaviorists blinded to surgery and experimental treatments. NP pain was accompanied by affective-like behaviors associated with anxiety, stress and depression using the forced swim stress and light-dark test paradigms, which were blocked by KOR antagonist JDTic. NP mice also exhibit enhanced aversion to KOR agonist, U50488, indicating enhanced KOR signaling in chronic pain.

To characterize components of KOR signaling in the amygdala in the NP pain state, we examined KOR mRNA expression and functional activity of the KOR. Using qRT-PCR, we found that NP pain mice exhibit a significant increase in KOR gene expression in the amygdala and bed nucleus of the stria terminalis (BNST). Using [35S]-GTPγS autoradiography, KOR agonist (U50488)-induced receptor activation was significantly increased in the medial (MeA), central amygdala (CeA) and BLA of NP pain compared to control surgery groups. Furthermore, *in situ* hybridization the KOR encoding gene *oprk1* within the amygdalar subnuclei was performed to determine whether the KOR message was upregulated in glutamatergic or GABAergic neuronal subpopulations.

Our data demonstrate that KOR expression and function are significantly increased in the amygdala of chronic NP pain animals. The upregulation of KOR in these brain regions that mediate emotional leaning may lead to the genesis of negative affect in chronic pain. Furthermore, the emotional component of pain is a significant predictor of quality of life for chronic pain patients, KOR antagonists may be an important therapeutic target for improving treatment of chronic pain.

Disclosures: A.L. Severino: None. **S. Liu:** None. **S. Pickens:** None. **R. Karmouta:** None. **H. Nasef:** None. **F.M. Leslie:** None. **F.I. Carroll:** None. **C.J. Evans:** None. **C.M. Cahill:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.10/AAA15

Topic: G.07. Other Psychiatric Disorders

Title: The atypical antipsychotics amisulpride and clozapine do not share discriminative stimulus properties in C57BL/6 mice

Authors: *F. ZHANG[1], R. RICE[1], T. M. HILLHOUSE[2], H. NANGUNURI[1], K. A. WEBSTER[1], A. N. BALDWIN[1], T. J. DONAHUE[1], J. H. PORTER[1]
[1]Psychology, Virginia Commonwealth Univ., Richmond, VA; [2]Psychology & Neurosci., Weber State Univ., Ogden, UT

Abstract: The benzamide derivative amisulpride (Solian) is an atypical antipsychotic used in Europe and most English speaking countries (except Canada and United States) to treat schizophrenia. Interestingly, at low doses it is also used to treat dysthymia. While its antipsychotic effects are believed to be via blockade of postsynaptic dopamine (DA) D_2 and D_3 receptors in the limbic system, its antidepressant effects are thought to be due to preferential blockade of presynaptic DA D_2 and D_3 receptors (Schoemaker et al 1997; Donahue et al 2014, 2017). Unlike the atypical antipsychotic clozapine, amisulpride has a fairly selective binding profile. In addition to its high binding affinity at DA D_2 and D_3 receptors, it has a high binding affinity at serotonin 5-HT_{7A} and 5-HT_{2B} receptors. We previously reported that in C57BL/6 mice trained to discriminate 10 mg/kg (s.c.) amisulpride from vehicle that clozapine did not generate amisulpride-appropriate lever responding (Donahue et al 2017). In the present study adult male C57BL/6 mice were trained to discriminate 1.25 mg/kg clozapine from vehicle in a two-lever food reinforcement procedure. After the clozapine generalization curve was established, amisulpride was tested for substitution at doses of 20, 40 and 80 mg/kg (s.c.). Amisulpride produced only vehicle-appropriate responding with a maximum of 5.1% clozapine-lever responding at 80 mg/kg with no significant decrease in response rates. These findings confirm our previous results that amisulpride and clozapine do not share discriminative stimulus properties in C57BL/6 mice trained to discriminate amisulpride. These results also confirm findings in rats trained to discriminate 5.0 mg/kg clozapine that amisulpride does not substitute for the clozapine cue (Goudie and Taylor 1998). While the exact mechanisms mediating amisulpride's discriminative stimulus remain to be determined, it is clear from the present and previous studies that amisulpride's discriminative cue properties are not shared by other antipsychotic drugs (either atypical or typical) and that it possesses a unique discriminative cue.

Disclosures: F. Zhang: None. **R. Rice:** None. **T.M. Hillhouse:** None. **H. Nangunuri:** None. **K.A. Webster:** None. **A.N. Baldwin:** None. **T.J. Donahue:** None. **J.H. Porter:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.11/AAA16

Topic: G.07. Other Psychiatric Disorders

Support: Nancy Lurie Marks Family Foundation to Z.Y.
NIH Grant MH112237 to Z.Y.
SUNY Buffalo PPBS to B.R.

Title: Chemogenetic activation of prefrontal cortex rescues synaptic and behavioral deficits in a mouse model of 16p11.2 deletion syndrome

Authors: *B. A. REIN, W. WANG, F. ZHANG, T. TAN, P. ZHONG, Z. YAN
Physiol. & Biophysics, SUNY Univ. At Buffalo, Buffalo, NY

Abstract: Microdeletion of the human 16p11.2 gene locus has been linked to Autism spectrum disorder (ASD) and intellectual disability, and confers risk for a number of other neurodevelopmental deficits. Transgenic mice carrying 16p11.2 deletion (*16p11*$^{+/-}$) display phenotypes reminiscent of those in human patients with 16p11.2 deletion syndrome, but the molecular mechanisms and treatment strategies for these phenotypes remain unknown. In this study, we have found that bothmale and female *16p11*$^{+/-}$mice exhibit deficient NMDA receptor (NMDAR) function in the medialprefrontal cortex (mPFC), a brain region critical for high level "executive" functions. Elevating the activity of mPFC pyramidal neurons with a CaMKII-driven Gq-coupled Designer Receptor Exclusively Activated by Designer Drugs (Gq-DREADD) led to the restoration of NMDAR function and the amelioration of cognitive and social impairments in *16p11*$^{+/-}$mice. These results suggest that NMDAR hypofunction in PFC may contribute to the pathophysiology of 16p11.2 deletion syndrome, and that restoring PFC activity is sufficient to rescue the behavioral deficits.

Disclosures: B.A. Rein: None. **W. Wang:** None. **F. Zhang:** None. **T. Tan:** None. **P. Zhong:** None. **Z. Yan:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.12/AAA17

Topic: G.07. Other Psychiatric Disorders

Title: The influence of molecular dentate gyrus lesion on behavior and mossy fiber - CA3 synapses in mice

Authors: *F. DYBOWSKI[1], C. A. TAMMINGA[2]
[1]UT Southwestern Med. Ctr., Dallas, TX; [2]Univ. of Texas Southwestern Med. Ctr. at Dallas, Dallas, TX

Abstract: Psychosis, a predominant symptom domain of schizophrenia, has been characterized in human in vivo imaging and post-mortem studies by decreased hippocampal GluN1 expression in dentate gyrus (DG), CA3 subfield hyperactivity and increased synaptic plasticity markers. Thorny excrescences (TE) constituting the mossy fiber-CA3 synaptic connections have been deemed a tunable gain control of excitatory input and were found increased in post-mortem studies. We hypothesize that drug treatment may reverse the CA3 subfield hyperactivity and abnormal TE morphology, which could lead to reversal of psychosis-like behavioral phenotypes. In order to test that, we administered clozapine to male GluN1 DG-specific knock-out (at least 4 months old) mice. As a measurable output, we looked at the morphology of TEs and performed a battery of behavioral tests split into two cohorts, N=12/group. The behavioral test battery consisted of contextual and cued fear conditioning, open field test, elevated plus maze, pre-pulse inhibition, social recognition memory. Golgi-Cox staining was used to analyze the morphology of TEs and measure total area. These experiments, which are still ongoing, will provide a broad perspective regarding the antipsychotic mechanism underlying current pharmacotherapies and may suggest novel targets for emerging drugs.

Disclosures: F. Dybowski: None. **C.A. Tamminga:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.13/AAA18

Topic: G.07. Other Psychiatric Disorders

Title: Altered cortical development and neural excitability in the medial prefrontal cortex of B-cell CLL/lymphoma 9 mutant mice

Authors: *Y. KUANG
Shanghai Jiaotong Univ., Shanghai City, China

Abstract: B-cell CLL/lymphoma 9 (*BCL9*), located on the human chromosome locus 1q21.1, has been implicated in tumor progression through the Wnt signaling pathway. Human genetic studies have suggested that common *BCL9* variants confer a risk of schizophrenia, bipolar disorder, and autism development. However, the function of BCL9 in central nervous system remains poorly understood. We used in utero electroporation mice and BCL9 mutant mice in our study. Here, we demonstrated BCL9 is highly expressed in mouse brain during the embryonic and early postnatal period. Knockdown BCL9 in E13.5 could severely disturb the migration of cortical neurons and down regulation of Wnt target genes. Knockdown of BCL9 increased ultrasonic vocalization in pups. Interestingly, we identify BCL9 expression level change voltage-dependent sodium channels expression, leading to abnormal neuronal excitability. We also noted that the common BCL9 variants regulate the brain structural volume and psychotic-like symptoms in adolescents. In conclusion, our findings indicate a possible role of BCL9 in the pathogenesis of neurodevelopmental disorders.

Disclosures:

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.14/AAA19

Topic: G.07. Other Psychiatric Disorders

Support: PRIN2012JTX3KL

Title: Effects of the satiety signal oleoylethanolamide on binge-like food consumption in female rats

Authors: A. ROMANO[1], M. V. MICIONI DI BONAVENTURA[2], C. GALLELLI[1], J. KOCZWARA[1], M. E. GIUSEPPONI[2], E. MICIONI DI BONAVENTURA[2], C. D'ADDARIO[3], T. CASSANO[4], S. GAETANI[1], *C. CIFANI[2]
[1]Dept of Physiol. and Pharmacol., Sapienza Univ. of Rome, Roma, Italy; [2]Univ. of Camerino, Sch. of Pharm., Camerino, Italy; [3]Univ. of Teramo, Teramo, Italy; [4]Dept. of Clin. and Exptl. Medicine, Univ. of Foggia, Foggia, Italy

Abstract: Several lines of evidence document the association between eating disorders and modern lifestyle, encompassing calorie-rich diets and psychological stress. Binge-eating disorder

(BED) is a eating disorder characterized by excessive consumption of food in a short period of time, along with loss of control and psychological distress. Among the networks that partake in the neurobiological bases of BED a large body of evidence supports the activation of the hypothalamic-pituitary-adrenal stress (HPA) axis. Pharmacological treatments for BED are limited thus highlighting the need to identify novel targets that could lead to the development of more effective therapies. A large body of evidence has accumulated on the role played by the lipid signal oleoylethanolamide (OEA) as a pharmacological target for controlling aberrant eating disorders. As a drug, OEA reduces food intake and body weight gain in laboratory rodents by inducing a state of satiety. Additionaly, OEA dampens the hyperactivity of the HPA axis and ameliorates the effects of stress. On the bases of these premises, in the present study we investigated the effects of OEA on high palatable food (HPF) intake in a rat model of BED. Moreover, we assessed the impact of OEA on the corticotropin-releasing factor (CRF) system which plays a critical role in stress and on the oxytocinergic system which is crucial in mediating the pro-satiety effect of OEA. We used female rats with a history of intermittent food restriction which show binge-like palatable food consumption after the exposure to a “frustration stress”. On the test day, we either exposed or did not expose the rats to the sight of the palatable food (frustration stress) before assessing food consumption. OEA was administered at three different doses (2.5, 5, 10 mg/kg i.p.) and HPF intake was monitored over 2h. After the behavioural experiment brains were collected and *in-situ* hybridization experiment was performed to analyse CRF and oxytocin mRNA expression in selected brain areas. Our results demonstrate that OEA (10 mg/kg) was able to selectively prevent binge eating; the antibinge effect was accompained by a reduction of CRF mRNA within the central-amygdala. Finally, in keeping with our previous observations we found that the antibinge effect of OEA was accompanied by a significant increase of oxytocin mRNA at hypothalamic level. In the current study, we provide for the first time evidence to support that the endogenous fatty-gut lipid OEA exerts a selective inhibitory effects on binge-like eating behavior in female rats, supporting the hypothesis that OEA might represent a novel potential pharmacological target for the treatment of aberrant eating patterns.

Disclosures: A. Romano: None. **M.V. Micioni Di Bonaventura:** None. **C. Gallelli:** None. **J. Koczwara:** None. **M.E. Giusepponi:** None. **E. Micioni Di Bonaventura:** None. **C. D'Addario:** None. **T. Cassano:** None. **S. Gaetani:** None. **C. Cifani:** None.

Poster

684. Other Psychiatric Disorders II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 684.15/AAA20

Topic: G.05. Anxiety Disorders

Support: NIH/NINDS Grant 1UH3NS100549-01

Title: Electrophysiological markers of distress in neuropsychiatric illness

Authors: *E. MATTESON[1], N. R. PROVENZA[2], C. LOHMAN[1,3], A. BARRIOS-ANDERSON[4,3], N. MCLAUGHLIN[1,5,3], D. A. BORTON[2,5]
[2]Neuroengineering, [1]Brown Univ., Providence, RI; [3]Butler Hosp., Providence, RI; [4]The Warren Alpert Med. Sch. of Brown Univ., Providence, RI; [5]Carney Inst. for Brain Sci., Providence, RI

Abstract: Adaptive deep brain stimulation (DBS) has the potential to offer improved therapy for neuropsychiatric illnesses by sensing changes in neural activity and adjusting stimulation parameters in response. Such a system should ideally be able to detect the onset of acute distress caused by, for instance, an environmental trigger, so that it can react by increasing stimulation amplitude. In the search for biomarkers that can be used to control adaptive DBS, we record electroencephalography (EEG) while patients perform a novel symptom provocation task that uses physical objects to elicit varying levels of distress, time-locked to EEG signals. We report behavioral and EEG analysis of task performance by patients with specific phobia, patients with obsessive compulsive disorder, and healthy controls.

Disclosures: E. Matteson: None. **N.R. Provenza:** None. **C. Lohman:** None. **A. Barrios-Anderson:** None. **N. McLaughlin:** None. **D.A. Borton:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.01/AAA21

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA019688

Title: Genetic effects on mu-opioid receptor ligand biased signaling

Authors: *X. ZHANG[1], S. HUTCHINS[2], R. GILMORE[2], E. VALLENDER[2]
[1]Program in Neurosci., [2]Dept. Psychiatry and Human Behavior, Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: The opioidergic system has been associated with motivation, reward, emotion, response to stress and pain. Specific genetic mutations in Mu-opioid receptors (OPRM1) have been shown in humans and nonhuman primates to affect pharmaceutical response and the propensity towards substance abuse; however, the specific mechanism by which these polymorphisms exert their effects remain largely unknown. Characterization of the second messenger signaling profile of OPRM1 alleles will further our understanding on molecular basis of associated behaviors and assist in the development of personalized therapeutic OPRM1 ligands. In this study, we explore whether ligand-induced GPCR downstream signaling pathways

are biased across OPRM1 polymorphisms. Two single nucleotide polymorphisms (SNPs) that change protein sequence, C17T and A118G, exist on the OPRM1 N-terminal domain and are common in human populations. Additionally, we are testing a rhesus macaque SNP, C77G, which appears to be functionally and behaviorally parallel. We first transduce transcriptional response element inducible luciferase reporters from four pathways (NFkB, cAMP, MAPK/ERK and MAPK/JNK) into multiple cell lines (SK-N-MC, CHO and HEK 293). We then transfect in a plasmid containing the specific variant of OPRM1 and generate a concentration response curve with DAMGO, beta-endorphin, morphine, and additional ligands. Preliminary data demonstrated that the potency of ligands on each downstream signaling pathways are different and this ligand bias is dependent on genetic polymorphisms, which indicates the existence of an interaction between genetics and ligands on the OPRM1 second massenger signaling pathways. Further, these ligand biased signaling profiles and their genetic influences are paralleled between rhesus macaques and humans, which contributing to the translational utility of these nonhuman primates as preclinical platform for personalized ligand design. Overall, this study has shown the effect of genetic polymorphisms on second messenger signaling recruitment by the OPRM1. These findings have implications not only important for understanding the means by which OPRM1 affects behaviors, but also cruical for how genetic polymorphisms at OPRM1 are likely to differentially affect novel biased ligands.

Disclosures: X. Zhang: None. **S. Hutchins:** None. **R. Gilmore:** None. **E. Vallender:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.02/AAA22

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA K99 DA043573
NIDA R01 DA037927

Title: Systems genetics discovery of genetic, genomic, and gene-by-environment mechanisms driving substance use and sensation seeking

Authors: *P. E. DICKSON[1], T. A. ROY[1], T. D. WILCOX[1], G. MITTLEMAN[2], E. J. CHESLER[1]
[1]The Jackson Lab., Bar Harbor, ME; [2]Psychological Sci., Ball State Univ., Muncie, IN

Abstract: Substance abuse is a critical public health issue with genetic and environmental causes. Sensation seeking is a multifaceted, heritable trait which predicts the development of substance use and abuse in humans, and similar phenomena have been observed in rodents. Genetic correlations among substance use and sensation seeking indicate shared biological

mechanisms. Environmental enrichment attenuates both traits suggesting that effects occur through these shared mechanisms. The molecular and neurobiological mechanisms underlying these relationships remain elusive. We used a systems genetics approach in BXD recombinant inbred (RI) mice to identify (1) genetic mechanisms driving intravenous cocaine self-administration and (2) shared genetic mechanisms underlying operant sensation seeking and alcohol preference. To assess the feasibility of using the BXD RI panel to discover the mechanisms through which environmental factors influence the shared mechanisms underlying substance use and sensation seeking, we quantified the effects of environmental enrichment on operant sensation seeking, preference for a novel environment, and locomotion in a novel environment in the C57BL/6J and DBA/2J inbred strains, the founder strains of the BXD RI panel. We identified strain-dependent effects of housing condition on each of these distinct indexes of sensation seeking. Collectively, these data provide novel and, in some cases, shared biological mechanisms driving substance use and sensation seeking in the BXD RI mouse panel and provide evidence of genotype-dependent effects of environmental enrichment on sensation seeking traits in the BXD founder strains.

Disclosures: P.E. Dickson: None. **T.A. Roy:** None. **T.D. Wilcox:** None. **G. Mittleman:** None. **E.J. Chesler:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.03/AAA23

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant U01DA04163202

Title: Utilizing the BxD genetic reference panel to identify the causal genetic variants of nicotine withdrawal deficits in hippocampal learning

Authors: L. R. GOLDBERG[1], M. G. KUTLU[2], D. ZEID[1], L. SEEMILLER[1], S. GADIWALLA[1], *T. J. GOULD[1]
[1]Biobehavioral Hlth., Penn State, University Park, PA; [2]Dept. of Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Cognitive deficits, such as disrupted learning, are a major symptom of nicotine withdrawal. These deficits are heritable, yet the genetic basis is unknown. Mice are valuable for identifying novel genes that contribute to variation in traits associated with various stages of addiction, including withdrawal. Our lab has developed a mouse model of nicotine withdrawal deficits in hippocampus-dependent learning, using chronic nicotine exposure via osmotic minipumps and contextual fear conditioning. Previously, we identified differences between

C57BL/6J and DBA2/J mice in cognitive deficits during nicotine withdrawal. Here, we aimed to utilize the recombinant inbred BXD genetic reference panel to identify novel genetic variants underlying nicotine withdrawal deficits in learning. Male and female mice (n=6-11 per sex per strain, 31 strains) received either chronic saline or nicotine (6.3 mg/kg per day for 12 days), and then were tested for hippocampus-dependent learning deficits using contextual fear conditioning. Additionally, using publically available data from GeneNetwork, we identified genetic correlations between nicotine withdrawal deficits in learning and locomotor stimulant response to phencyclidine (PCP) and cocaine, with strains that were less sensitive to stimulant withdrawal-induced cognitive deficits also being shown to be less sensitive to stimulant-induced increases in locomotor activity. Quantitative trait locus (QTL) mapping analyses using GeneNetwork (1000 permutations) identified a significant QTL on chromosome 4 (82.4 Mb, LRS =23.74, $p<0.05$). To prioritize candidate genes, we utilized publicly available hippocampal gene expression data from naive animals to identify potential cis-eQTL. We identified 4 positional candidates (*Ptprd*, *Tyrp1*, *2310067E19Rik*, *Nfib*) that overlapped with our behavioral QTL and correlated with our behavioral data. To expand upon these positional candidates and identify hippocampal transcriptome changes associated with nicotine withdrawal, we will soon complete mRNA-sequencing in the BXD lines exhibiting extreme phenotypic variation.

Disclosures: L.R. Goldberg: None. **M.G. Kutlu:** None. **D. Zeid:** None. **L. Seemiller:** None. **S. Gadiwalla:** None. **T.J. Gould:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.04/AAA24

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 MH104603-01 (to MB)

Title: Sex-dimorphic gene x environment interactions predict tobacco and cannabis lifetime use

Authors: *M. BORTOLATO[1,2,3], S. BROWN[2,4], W. HOSSAIN[2,5], A. M. MANZARDO[2,5], M. G. BUTLER[2,5], P. J. FITE[2,4]
[1]Pharmacol. and Toxicology, Univ. of Utah, Salt Lake City, UT; [2]Consortium for Translational Res. on Aggression and Drug Abuse (ConTRADA), [3]Pharmacol. and Toxicology, [4]Clin. Child Psychology Program, Univ. of Kansas, Lawrence, KS; [5]Departments of Psychiatry, Behavioral Sci. and Pediatrics, Univ. of Kansas Med. Ctr., Lawrence, KS

Abstract: Post-secondary students in Western countries exhibit a high prevalence of cannabis and tobacco use disorders. The etiology of these problems is contributed by several psychosocial factors, including childhood adversity and trauma. The mechanisms whereby these

environmental determinants predispose to the use of these substances, however, remain elusive, due to our poor knowledge of genetic and biological moderators. Recent evidence points to the monoamine oxidase A (*MAOA*) gene as a moderator of the effects of lifetime stress on the initiation of substance use. Building on these premises, in the present study we analyzed whether *MAOA* upstream variable number tandem repeat *(u-VNTR)* alleles interact with child maltreatment history to predict for lifetime cannabis and tobacco consumption. Five hundred college students (age: 18-25 years) from a large Midwestern University were surveyed for their child maltreatment history (encompassing emotional, physical, and sexual abuse, as well as emotional and physical neglect) and lifetime consumption of cannabis and tobacco. Saliva samples were obtained to determine the *MAOA u-VNTR* genotype of each participant. In female students, lifetime tobacco and cannabis use was predicted by the interaction of physical and emotional abuse with high-activity *MAOA* allelic variants; conversely, in males, the interaction of low-activity *MAOA* alleles and physical abuse was associated with lifetime use of tobacco, but not cannabis. These findings collectively suggest that the vulnerability to smoke tobacco and cannabis is predicted by sex-dimorphic interactions of *MAOA* gene with childhood abuse. These biosocial underpinnings of tobacco and cannabis use disorders may prove important in the development of novel personalized interventional strategies for college age students.

Disclosures: M. Bortolato: None. **S. Brown:** None. **W. Hossain:** None. **A.M. Manzardo:** None. **M.G. Butler:** None. **P.J. Fite:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.05/AAA25

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant P50DA037844

Title: Effects of environmental enrichment on behavioral measures of behavioral regulation in heterogeneous stock rats

Authors: *K. ISHIWARI[1], A. M. GEORGE[1], C. D. MARTIN[1], P. J. MEYER[2], O. POLESSKAYA[3], A. A. PALMER[3], J. B. RICHARDS[1]
[1]Res. Inst. on Addictions, [2]Psychology, Univ. at Buffalo, Buffalo, NY; [3]Psychiatry, UCSD, La Jolla, CA

Abstract: Environmental enrichment has been shown to produce a variety of beneficial neurobehavioral effects in animal models of neuropsychiatric disorders that are associated with maladaptive dysregulation of behavior, such as ADHD, autism, and substance abuse. The present study investigated the effects of environmental enrichment in N/NIH heterogeneous stock (HS)

rats. We examined behavioral measures of psychological traits thought to underlie behavioral regulation and, when dysregulated, predispose individuals to drug abuse. Male HS rats were reared in pairs in standard plastic laboratory cages (n=200) or in groups of 16 in a complex environment consisting of a large multi-level cage filled with pet toys (n=64) starting at approximately postnatal day 30. The two groups were compared for their performance on a battery of behavioral tasks designed to measure various aspects of behavioral regulation (i.e., sensation/novelty seeking, social approach, attentional control, inhibitory control, and impulsive decision making). Specifically, the rats were tested on locomotor response to novelty, light reinforcement, social reinforcement, choice reaction time, and delay discounting tasks. Our results indicated that, compared to the rats reared in standard laboratory cages, the rats housed in the complex environment displayed reduced locomotor response to novelty, reduced operant responding to light and social stimuli, enhanced sustained attention, and enhanced inhibitory control. In addition, their locomotor activity and operant responding habituated more rapidly. However, the results of the delay discounting test, which employed a sequential patch choice procedure, indicated that rats housed in the complex environment discounted delayed water reinforcements more steeply (i.e., "were more impulsive"). Nevertheless, the enriched rats also had higher water consumption rates, suggesting that they were more efficient in their responding and thus better maximized their water intake; this could be viewed as greater behavioral plasticity. Taken together, the present results indicate that, compared to the rats pair-housed in standard laboratory cages, the rats group-housed in the complex environment were able to filter out irrelevant stimuli more effectively (e.g., greater habituation) and thereby regulate their behavior more efficiently (e.g., maximized water intake). Our results suggest that use of standard plastic cages dramatically influences behavior. In future studies, we hope to explore whether these effects compromise the translational validity of animal behavioral studies.

Disclosures: K. Ishiwari: None. **A.M. George:** None. **C.D. Martin:** None. **P.J. Meyer:** None. **O. Polesskaya:** None. **A.A. Palmer:** None. **J.B. Richards:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.06/AAA26

Topic: G.08. Drugs of Abuse and Addiction

Support: P50DA037844

Title: Genetic analysis of multiple measures of locomotor activity in 2,325 outbred heterogeneous stock rats

Authors: *A. S. CHITRE[1], O. POLESSKAYA[1], J. GAO[1], A. HORVATH[2], A. HUGHSON[2], T. WANG[4], K. ISHIWARI[5], C. L. ST. PIERRE[7], H. WLADECKI[1], R. CHENG[1], K. HOLL[8], J. A.

TRIPI[6], C. P. KING[6], P. MEYER[6], L. C. SOLBERG WOODS[9], T. E. ROBINSON[3], S. B. FLAGEL[2], H. CHEN[4], A. A. PALMER[1]
[1]Dept. of Psychiatry, Univ. of California San Diego, La Jolla, CA; [2]Dept. of Psychiatry and Mol. and Behavioral Neurosci. Inst., [3]Dept. of Psychology, Univ. of Michigan, Ann Arbor, MI; [4]Dept. of Pharmacol., The Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [5]Res. Inst. on Addictions, [6]Dept. of Psychology, Univ. at Buffalo, Buffalo, NY; [7]Dept. of Genet., Washington Univ., St. Louis, MO; [8]Med. Col. of Wisconsin, Milwaukee, WI; [9]Dept. of Intrnl. Med., Wake Forest Baptist Med. Ctr., Winston-Salem, NC

Abstract: Introduction: Locomotor behavior is important both because it is of significant biological interest in its own right and because it can sometimes confound other more complicated behavioral measures. We performed a genome-wide association study (**GWAS**) and examined genetic correlations across several cohorts in which locomotor activity was measured. **Methods**: The cohorts differed in many ways, including age, and procedural details like size of arena, lighting conditions and test duration. All subjects were N/NIH heterogeneous stock (**HS**) rats, which were derived from an intercross among 8 inbred rat strains and have been maintained as an outbred population for more than 80 generations. Locomotor traits were measured in three phenotyping centers: Center 1 (University of Michigan): Rats (*N=768, age= 77 days ± sd 5.45*) were placed in the middle of a 45 cm x 15 cm chamber. Noldus Ethovision software was used to track the behavior of the rats for 25 min. Center 2 (University of Tennessee Health Sciences Center): Rats (*N= 665, age= 32 days ± sd 3.35*) were placed in a 100 cm x 100 cm chamber. Noldus Ethovision software was used to track the behavior of the rats for 60 min. Center 3 (University at Buffalo, Research Institute on Addictions): Rats (*N= 891, age= 70 days ± sd 7.24*) were placed in a 24 cm x 45 cm chamber. Beam breaks were used to track the behavior of the rats for 18 min. We used a genotype by sequencing approach to obtain > 6 million SNPs per individual. To detect the genetic basis of these behavioral traits, we estimated the proportion of variance attributable to SNP genotypes (SNP heritability h^2) using GCTA-GREML. We used the GCTA Bivariate GREML analysis to estimate the genetic correlation (*rG*). We performed GWAS using the linear mixed model approach, implemented in the software GEMMA. **Results**: SNP heritability estimates ranged from 0.24 to 0.42. The genetic correlation between centers 1 and 3 were high (0.84 ± se .12), the genetic correlation between centers 2 and 3 was moderate (0.46 ± se .15) and the genetic correlation between centers 1 and 2 was low (0.11 ± se .19).
Discussion: Center 2, which showed the lowest correlations, included younger animals, used a larger open field, and included a longer test than centers 1 and 3; these factors may account for the low correlations between center 2 and centers 1 and 3. Ongoing studies will include a joint GWAS analysis of at least centers 1 and 3; the final sample size of that analysis should be greater than 3,000 and will thus have power to identify loci that account for as little as 1% of total trait variance.

Disclosures: O. Polesskaya: None. **J. Gao:** None. **A. Horvath:** None. **A. Hughson:** None. **T. Wang:** None. **K. Ishiwari:** None. **C.L. St. Pierre:** None. **H. Wladecki:** None. **R. Cheng:** None. **K. Holl:** None. **J.A. Tripi:** None. **C.P. King:** None. **P. Meyer:** None. **L.C. Solberg Woods:** None. **T.E. Robinson:** None. **S.B. Flagel:** None. **H. Chen:** None. **A.A. Palmer:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.07/BBB1

Topic: G.08. Drugs of Abuse and Addiction

Support: P50DA037844

Title: Genome-wide association study of behavioral regulation traits in outbred heterogeneous stock rats

Authors: *C. D. MARTIN[1,2], K. ISHIWARI[3], A. M. GEORGE[4], P. MEYER[5], A. S. CHITRE[6], O. POLESSKAYA[7], A. A. PALMER[8], J. B. RICHARDS[4]
[1]Psychology, Univ. at Buffalo Dept. of Psychology, Buffalo, NY; [2]Res. Inst. on Addictions, Buffalo, NY; [3]Res. Inst. on Addictions, Univ. at Buffalo, Buffalo, NY; [4]Res. Inst. On Addictions, Buffalo, NY; [5]Psychology, Univ. At Buffalo, Buffalo, NY; [6]Psychiatry, Univ. of California San Diego, La Jolla, CA; [7]Year, San Diego, CA; [8]Psychiatry, UCSD, La Jolla, CA

Abstract: Behavioral regulation increases fitness. Adequate regulation of behavior allows animals to respond in an adaptive fashion to environmental changes. Dysregulation of behavior predisposes animals to maladaptive behaviors such as ADHD, autism, drug abuse, and more. Behavioral regulation was measured in a preliminary cohort of 791 N/NIH male and female heterogeneous stock (HS) rats.
Our assessment of behavioral regulation included five behavioral tests; i.) Locomotor response to a novel environment, ii.) Sensory (light) reinforcement, iii.) Social reinforcement, iv.) Reaction time; and v.) Delay-discounting in a patch foraging model. Locomotor response to novelty and light reinforcement are measures of sensation seeking. Social reinforcement plays an important role in facilitating normal social relationships. The reaction time task tested attentional control and preventing distraction by irrelevant stimuli. The delay discounting model of patch foraging tested the rats' ability to make an efficient decision about future rewards and to avoid making maladaptive, impulsive choices. We used a genotyping by sequencing approach to obtain 6 million SNPs per individual rat. To detect the genetic basis of these behavioral traits, we estimated the proportion of variance attributable to SNP genotypes (SNP heritability h2) using GCTA-GREML. A total of 1600 HS rats will be tested by the conclusion of the study. Multiple phenotypes were taken for all of the tasks. Significant heritability was found for the locomotor, light reinforcement, reaction time, and delay discounting tasks. Heritability was highest for locomotor traits (0.31 + 0.05 for total distance).
Other behaviors had moderate heritabilities; 0.27 + 0.06 for mean reaction time; 0.25 + 0.07 for response to social reinforcement; 0.24 + 0.05 for response to light reinforcement; 0.17 + 0.05 for indifference point on delay discounting; 0.34 + 0.06 for series of delays on delay discounting.

Genetic correlations were calculated for pairs of traits to account for pleiotropic effect. Presently, genome-wide association analysis is ongoing, identifying genetic loci implicated in behavioral traits.
Highly genetically correlated traits can be analyzed together, further increasing power to detect loci explaining smaller proportion of total variance.

Disclosures: C.D. Martin: None. **K. Ishiwari:** None. **A.M. George:** None. **P. Meyer:** None. **A.S. Chitre:** None. **O. Polesskaya:** None. **A.A. Palmer:** None. **J.B. Richards:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.08/BBB2

Topic: G.08. Drugs of Abuse and Addiction

Support: R01 DA039168 (C.D.B.)
F31 DA040324 (N.Y.)
T32 GM008541
Burroughs Wellcome Fund: Boston University's Transformative Training Program in Addiction Science (TTPAS)

Title: Deciphering the molecular mechanisms underlying heterogeneous nuclear ribonucleoprotein H1 (hnRNP H1) regulation of methamphetamine-induced dopamine release and addictive behaviors

Authors: *Q. RUAN[1], N. YAZDANI[1], J. BEIERLE[1], K. ZHENG[1], J. J. CHEUNG[1], M. A. COELHO[4], E. A. FULTZ[4], A. F. HEALY[4], F. MORTAZAVI[2], W. LIN[3], P. E. A. ASH[1], D. L. ROSENE[2], A. EMILI[3], B. WOLOZIN[1], K. K. SZUMLINSKI[4], C. D. BRYANT[1]
[1]Pharmacol. and Exptl. Therapeut., [2]Dept. of Anat. and Neurobio., [3]Ctr. for Network Systems Biol., Boston Univ. Sch. of Med., Boston, MA; [4]Dept. of Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: We mapped and validated Hnrnph1 (heterogeneous nuclear ribonucleoprotein H1) as a quantitative trait gene underlying reduced methamphetamine-induced locomotor activity, reward, reinforcement, and dopamine release. Specifically, Hnrnph1 deletion blunted the ability of methamphetamine (MA) to induce and increase extracellular level of dopamine in the nucleus accumbens which was accompanied by a reduction in the level of dopamine metabolite, DOPAC. Importantly, MA-induced glutamate release was not impacted, indicating a dopamine-selective mechanism. To identify the molecular mechanism underlying Hnrnph1 regulation of methamphetamine behavior and dopamine transmission, we hypothesized that a decrease in the number or innervation of dopaminergic neurons could underlie the neurobehavioral results.

However, our results indicated that tyrosine hydroxylase (TH, a precursor for dopamine synthesis and a marker of dopaminergic neurons) immunostaining via immunohistochemistry and Western blot in the striatum and midbrain was increased in Hnrnph1+/- mice in comparison to wildtype. These data suggest an alternate, drug-induced cell biological mechanism by which Hnrnph1 deletion affects the MA neurobehavioral response. MA enters presynaptic dopaminergic neurons via the dopamine transporter (DAT) and dopamine-containing vesicles via the vesicular monoamine transporter (VMAT) to increase synaptic dopamine levels. We tested the hypothesis that MA would induce a translocation of hnRNP H1 from the nucleus to the cytoplasm. We found a marked 2.4-fold increase in the level of synaptic hnRNP H in the striatum of Hnrnp1+/- mice compared to that of the wildtype. Cellular fractionation of striatal tissue indicated a reduction in the level of cytoplasmic hnRNP H in Hnrnph1+/- mice versus the wildtype, which suggested potential mobilization of hnRNP H from the cytoplasm to the synapse. In addition, preliminary findings indicate that MA treatment induces an increase in cytoplasmic but not nuclear hnRNP H in Hnrnph1+/- in comparison to WT mice. Ongoing studies continue to focus on synaptic function of hnRNP H1 in regulating drug-induced dopamine release and behavior using proteomic analysis of synaptic hnRNP H-associated complexes.

Disclosures: Q. Ruan: None. **N. Yazdani:** None. **J. Beierle:** None. **K. Zheng:** None. **J.J. Cheung:** None. **M.A. Coelho:** None. **E.A. Fultz:** None. **A.F. Healy:** None. **F. Mortazavi:** None. **W. Lin:** None. **P.E.A. Ash:** None. **D.L. Rosene:** None. **A. Emili:** None. **B. Wolozin:** None. **K.K. Szumlinski:** None. **C.D. Bryant:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.09/BBB3

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH: U01DA044399-01 (G. Peltz)
T32 GM008541: Biomolecular Pharmacology Training Program, Boston University School of Medicine (D.H. Farb)
Burroughs Wellcome Fund: Boston University's Transformative Training Program in Addiction Science (TTPAS) (L. Farrer)

Title: Mouse inbred strain survey of oxycodone addiction traits in an opioid multi-stage addiction assessment paradigm

Authors: *J. A. BEIERLE[1], J. SCOTELLARO[1], J. KELLIHER[1], R. K. BABBS[1], M. ZHENG[2], G. PELTZ[2], C. D. BRYANT[3]

[1]Boston Univ., Boston, MA; [2]Stanford Univ., Stanford, CA; [3]Pharmacol. and Exptl. Therapeut., Boston Univ. Sch. of Med., Boston, MA

Abstract: Opioid use disorder (**OUD**) is a heritable addictive disorder that has reached epidemic proportions in the United States, yet its genetic etiology remains poorly understood. Murine forward genetic studies of addiction traits can identify novel genetic factors and biological pathways relevant to humans, leading to improved therapeutics. We are conducting a large strain survey of a panel of mouse inbred strains for oxycodone (**OXY**)-induced behaviors in our multi-stage addiction assessment protocol (**MSAAP**). Our long-term goal is to conduct high resolution haplotype association mapping of the genetic basis of opioid addiction traits. These traits include acute locomotor response, locomotor sensitization, conditioned place preference, extinction, analgesic tolerance, the emotional-affective component of opioid dependence, and several protracted cognitive and emotional-affective withdrawal phenotypes induced following a period of abstinence from chronic OXY administration. We have thus far tested 12 inbred strains (BALB/cJ, BALB/cByJ, C3H/HeJ, FVB/J, DBA/2J, NOD/ShiLtJ, CBA/J, C57BL/6J, 129s1/SvlmJ, A/J, NU/J, SJL/J). Notably, , we identified robust, male-specific BALB/c substrain differences in protracted withdrawal, including anxiety-like behavior in the light/dark box and head pokes in the hole-board test. We also identified robust differences in OXY hot plate analgesic tolerance between BALB/c substrains. These initial findings indicate that genetic differences in multiple complex behavioral traits are associated with different stages of opioid addiction. The observation of BALB/c substrain differences in protracted withdrawal is particularly promising, as their reduced genetic complexity facilitates rapid identification of novel genetic factors underlying behavioral addiction traits. Complete testing of 30 classical inbred strains will lead to the identification of high resolution genetic loci, candidate genes, and functional variants that will be confirmed via gene editing. Expression QTL mapping, pathway, and gene network analysis will inform the molecular mechanisms that bridge genetic variants with behavior.

Disclosures: J.A. Beierle: None. **J. Scotellaro:** None. **J. Kelliher:** None. **R.K. Babbs:** None. **M. Zheng:** None. **G. Peltz:** None. **C.D. Bryant:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.10/BBB4

Topic: G.08. Drugs of Abuse and Addiction

Support: R01 DA039168 (C.D.B.)
T32 GM008541: Biomolecular Pharmacology Training Program, Boston University School of Medicine (D.H. Farb)

Title: Reward threshold as measured via intracranial self-stimulation in Hnrnph1$^{+/-}$ mice showing reduced methamphetamine addictive behaviors

Authors: *K. N. BORRELLI[1], K. R. DUBINSKY[1], J. L. SCOTELLARO[1], E. H. CHARTOFF[2], W. A. CARLEZON, Jr[3], C. D. BRYANT[1]
[1]Pharmacol. and Exptl. Therapeut., Boston Univ. Sch. of Med., Boston, MA; [2]Harvard Med. Sch., Belmont, MA; [3]Dept Psychiat, Harvard Med. Sch./Mclean Hosp., Belmont, MA

Abstract: Substance abuse disorders are heritable, but the genetic basis remains largely unknown. Using quantitative trait locus (QTL) mapping, we identified heterogeneous nuclear ribonucleoprotein H1 (*Hnrnph1*) as a quantitative trait gene (QTG) underlying sensitivity to the locomotor stimulant properties of methamphetamine. Mice heterozygous for a frameshift deletion resulting in a premature stop codon in the first coding exon of Hnrnph1 (*Hnrnph1*$^{+/-}$) show reduced methamphetamine-induced locomotor activity and reduced methamphetamine oral self-administration. We are currently using intracranial self-stimulation (ICSS) to assess reward sensitivity at baseline and following methamphetamine administration in *Hnrnph1*$^{+/-}$ mice. ICSS is used to quantify threshold for self-administration of brain stimulation reward (BSR) delivered through an intracranial stimulating electrode. *Hnrnph1*$^{+/-}$ mice are currently undergoing a unilateral stereotaxic procedure to implant an electrode in the medial forebrain bundle (MFB). Mice will be trained on a fixed-ratio 1 (FR-1) schedule to respond for stimulation, such that a ¼ turn of a wheel manipulandum earns a 500ms train of rewarding stimulation followed by a 500ms timeout. Subjects will then be exposed to a series of descending stimulation frequencies at a set threshold current. Using a frequency-rate curve-shift approach, threshold frequencies required to produce responding will be determined for each animal at baseline and following administration of methamphetamine (0.5, 1.0, or 2.0 mg/kg, delivered intraperitoneally). Histological verification of electrode placement will be performed upon completion of ICSS experiment. Significant changes in ICSS reward threshold related to the *Hnrnph1* disruption would provide further support for its contribution to to the neurobiological mechanisms of stimulation-induced reward sensitivity and the neurobehavioral response to multiple drugs of abuse.

Disclosures: K.N. Borrelli: None. **K.R. Dubinsky:** None. **J.L. Scotellaro:** None. **E.H. Chartoff:** None. **W.A. Carlezon:** None. **C.D. Bryant:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.11/BBB5

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH-MH103455

Rutgers NJMS

Title: Cyfip1-mediated molecular mechanisms in the regulation of cocaine addiction

Authors: A. KAMALI TAFRESHI[1], K. PRASAD[1], G. BARBAYANNIS[1], A. TASLEEM[1], S. STRATTON[1], I. DENIZ[1], D. L. BENSON[2], *O. BOZDAGI[1]
[1]Psychiatry, Rutgers Univ., Newark, NJ; [2]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Structural and functional changes in the nucleus accumbens (NAc) are associated with addiction related behaviors such as cocaine seeking. New evidence on genetic risk factors can help elucidate the response to addictive drugs. Cytoplasmic FMR1-interacting protein (*CYFIP)1* has been identified as a risk factor for several neuropsychiatric disorders including schizophrenia, intellectual disability, and autism in humans. Recently *Cyfip2* was identified as a key regulator of locomotor responses to cocaine in mice. Cyfip2 and Cyfip1 are closely related family members, which function to repress protein translation through binding interactions with FMRP, and also to regulate actin cytoskeleton assembly as a component of WAVE regulatory complex. We have previously shown that mice carrying a *Cyfip1* mutation (*Cyfip1*$^{+/-}$) show dysregulated synaptic plasticity and Rac1-dependent enhanced presynaptic function during development in the hippocampus. To test our hypothesis that cocaine related behavioral responses and synaptic function in the NAc are affected when Cyfip1 levels are reduced, we performed open field tests and compared locomotor activity in control conditions and in response to cocaine by using an automated video tracking system. Wild type mice display an increase in locomotor response to the administration of cocaine (15mg/kg) in both genders, as expected. This response is blunted in all *Cyfip1*$^{+/-}$ mice and in male mice more than female. Preliminary data showing GluA1 immunolocalization in the NAc after cocaine injection indicate dysregulated GluA1 levels in *Cyfip1*$^{+/-}$ mice. In order to better simulate the pathophysiology of drug addiction in humans, we also performed a conditioned place preference paradigm, which show increased cocaine seeking in *Cyfip1*$^{+/-}$ mice. Field EPSP recordings in the NAc show comparable post-tetanic potentiation between genotypes. These findings provide a novel cellular mechanism that may contribute to cocaine-induced behavioral alterations. Clarifying Cyfip1's role in cocaine response, locomotor sensitization, and NAc plasticity, which is a previously unexamined target, may be relevant for a variety of disease-related genes with similar functions.

Disclosures: A. Kamali Tafreshi: None. **K. Prasad:** None. **G. Barbayannis:** None. **A. Tasleem:** None. **S. Stratton:** None. **I. Deniz:** None. **D.L. Benson:** None. **O. Bozdagi:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.12/BBB6

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA009815
NIDA Grant F31DA036322
NIH Grant DA036322
SAP Grant 4100055576

Title: Distinct mRNA profiles for reward devaluation, heroin addiction-like behavior and heroin-induced 'relapse' in the nucleus accumbens of vulnerable and resilient rats

Authors: *J. E. DOUTON[1], C. G. IMPERIO[1], A. J. MCFALLS[2], K. E. VRANA[2], W. M. FREEMAN[3], P. S. GRIGSON[1]
[1]Neural and Behavioral Sci., [2]Dept. of Pharmacol., Pennsylvania State University, Col. of Med., Hershey, PA; [3]Physiol., Oklahoma Univ. Hlth. Sci. Ctr., Oklahoma City, OK

Abstract: Understanding the underlying individual differences that lead some, but not others, to develop addiction can provide insight into substance use disorder and into potential treatments for the disease. In our model, rats have 5 min access to 0.15% saccharin followed by 6 h self-administration (SA) of either saline or heroin intravenously (iv). There are 16 such daily pairings followed by tests to assess drug seeking behaviors. In this paradigm, two subpopulations are observed, one that greatly suppresses intake of the heroin-paired saccharin cue (large suppressors) and one that accepts it (small suppressors). Importantly, greater avoidance of the cue is associated with greater addiction-like behaviors (ALBs) such as escalation of drug SA over trials, strong willingness to work for drug, greater seeking during extinction, and greater drug-induced reinstatement (Imperio & Grigson, 2015). Imperio et al. (2016) used next-generation sequencing (RNA-seq) and a subset of these rats to examine the nucleus accumbens (NAc) transcriptome in large suppressor, small suppressor, and saccharin-saline controls (n=5/group). Here, we have revisited this data set to identify genes whose expression is correlated 0.6 or greater (negatively or positively) with saccharin intake and the above described ALBs. In general, the results show that gene expression associated with reward devaluation and ALBs was not only different, but also opposite when overlapping. Specifically, the expression of 78 genes was positively correlated with intake of the saccharin cue, 40 of which were also negatively correlated with one or more of the ALBs and 38 genes unique to saccharin suppression. The expression of 15 genes was negatively correlated with intake of the saccharin cue, 7 of which were positively correlated with one or more of the ALBs and 8 unique to saccharin suppression. A set of only three genes (Orai2, Galc, Higd1b) was positively correlated, and a set of 9 genes (Aurkc, FAM105a, Loc1003637, Nif3l1, Pot1, Rad52, Rexo4, Tmem209, Tmem39b) negatively correlated, with all four ALBs including 1st h SA, 6 h SA, extinction, and PR responding. Finally, regarding heroin-induced reinstatement, the expression of 18 genes was correlated with the behavior and 3/10 of the positively correlated genes (Mir9-2, RDG1306227, and Colec12) also were negatively correlated with saccharin intake. Thus, when examining the mRNA expression of thousands of genes in the NAc of vulnerable and resilient rats, three distinct mRNA profiles were obtained for avoidance of the drug-paired cue, ALBs, and heroin-induced reinstatement, even though these behaviors are, themselves, highly correlated with one another.

Disclosures: J.E. Douton: None. **C.G. Imperio:** None. **A.J. McFalls:** None. **K.E. Vrana:** None. **W.M. Freeman:** None. **P.S. Grigson:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.13/BBB7

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH DP1 DA044250
Whitehall Foundation Grant (EAH)
Charles E Kaufman Foundation Young Investigator Award (EAH)

Title: Neuroepigenetic remodeling in cocaine addiction associated alternative splicing and behavior

Authors: *S.-J. XU[1], M. CARPENTER[2], Q. HU[3], S. LOMBROSO[2], S. MCCLORY[3], K. LYNCH[3], M. E. WIMMER[4], C. PIERCE[5], E. A. HELLER[6]
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Dept. of Systems Pharmacol. and Translational Therapeut., [3]Univ. of Pennsylvinia, Philadelphia, PA; [4]Psychology, Temple Univ., Philadelphia, PA; [5]Univ. Pennsylvania Sch. of Med., Philadelphia, PA; [6]Dept. of Systems Pharmacol. and Translational Therapeut., Perelman Sch. of Medicine, Univ. of Pennsyl, Philadelphia, PA

Abstract: Histone proteins and their associated DNA function to regulate gene expression in response to environmental changes. To date, numerous studies have implicated epigenetic remodeling of covalent histone posttranslational modifications (hPTMs) in addiction pathologies, yet the precise molecular mechanisms underlying such behavior remains unclear. We tested the hypothesis that trimethylation of histone H3 lysine 36 (H3K36me3) directly mediates alternative splicing in brain, to generate isoforms that facilitate the addiction phenotype. Previous work from our lab found that H3K36me3 enrichment significantly predicts splicing events (Hu et al. 2017) in the nucleus accumbens (NAc), a brain reward region. To further dissect this phenomenon, we injected NAc with HSV-SET2, a histone methyltransferase that catalyzes H3K36me3, or a catalytically-inactive control HSV-R195G, to induce H3K36me3. After confirming H3K36me3 enrichment by western blot and quantitative mass-spectrometry, we processed infected tissue using single sample sequencing (S3EQ) to generate H3K36me3 ChIP- and RNA-seq data from one tissue source to identify H3K36me3 associated alternative splicing events. We identified a subset of neuronal genes that show coincident cocaine-regulated H3K36me3 modification and alternative splicing, which we have validated with qPCR using radiolabeled probes. We are now poised to validate the direct causal relevance of H3K36me3 enrichment to splicing of these target exons, using CRISPR-mediated epigenetic editing (dCas9-SET2). Taken together, our work investigates a novel mechanism for chromatin-mediated

alternative splicing in brain in the context of cocaine addiction, supporting a critical role of epigenetic remodeling in neuronal gene expression, splicing and neuropathological behavior.

Disclosures: S. Xu: None. **M. Carpenter:** None. **Q. Hu:** None. **S. Lombroso:** None. **S. McClory:** None. **K. Lynch:** None. **M.E. Wimmer:** None. **C. Pierce:** None. **E.A. Heller:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.14/BBB8

Topic: G.08. Drugs of Abuse and Addiction

Support: ABS Graduate Student Grant

Title: Homeostatic mechanisms of alcohol-induced sleep disturbances in *Drosophila*

Authors: *M. E. RAMIREZ ROMAN[1], C. BILLINI[1], G. DE JESUS[1], D. BUFFILL[1], M. PEREZ[1], L. DE JESUS[1], J. L. AGOSTO[1], N. S. ATKINSON[2], A. GHEZZI[1]
[1]Dept. of Biol., Univ. of Puerto Rico, Rio Piedras Campus, San Juan, PR; [2]Univesity of Texas Austin, Austin, TX

Abstract: Exposure to alcohol is known to trigger homeostatic adaptations in the brain that lead to the development of drug tolerance and dependence. These adaptations are also believed to be the root of a collection of sleep disturbances that often manifest during the development of alcoholism. Because both, alcohol dependence and sleep modulation are under homeostatic regulation we hypothesize that these processes share common mechanisms. Here we use a Drosophila model system to test this hypothesis. We find that in Drosophila, acute alcohol exposure causes disturbances in sleep patterns that resemble those described in mammals. These disturbances include an increase in total sleep duration, decrease sleep latency, as well as an increased number of sleep episode per day (fragmented sleep). Furthermore we show that many of the genes implicated in the neural adaptations behind alcohol tolerance, have also been implicated in the regulation of sleep cycles. However, little is known about the direct pathways by which these biological mechanisms interact. In this study, we explore the effect that genes involved in synaptic homeostasis processes have on alcohol-induced sleep disturbances. Our results suggest that sleep and alcohol neuroadaptation share a common regulatory mechanism, and brings us closer to understanding the interaction between these two homeostatic processes.

Disclosures: M.E. Ramirez Roman: None. **C. Billini:** None. **G. de Jesus:** None. **D. Buffill:** None. **M. Perez:** None. **L. De Jesus:** None. **J.L. Agosto:** None. **N.S. Atkinson:** None. **A. Ghezzi:** None.

Poster

685. Genetic Influences on Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 685.15/BBB9

Topic: G.08. Drugs of Abuse and Addiction

Support: 5R25NS080687

Title: Analysis of ethanol and ketamine cross-drug interaction reveals potential targets for pharmaco-epigenetic intervention in drug addiction

Authors: *A. M. PADILLA[1], M. RAMÍREZ[3], C. BILLINI[4], M. FRANCIA[2], J. AGOSTO[2], A. GHEZZI[2]
[1]Cell and Mol. Biol., Univ. of Puerto Rico Rio Piedras, Guaynabo, PR; [2]Univ. of Puerto Rico Rio Piedras, San Juan, PR; [3]Univ. of Puerto Rico Río Piedras, San Juan, PR; [4]Univ. of Puerto Rico, San Juan, PR

Abstract: Sustained exposure to drugs leads to homeostatic adaptations in the brain brought on by changes in gene expression at synapses. This genetic plasticity is involved in the persistence of symptoms of drug addiction even after extended periods of abstinence and give rise to the behavioral phenotypes of tolerance and dependence. After exposure to sedatives such as alcohol, epigenetic modifications are known to activate the expression of synaptic proteins. 11 genes acetylated as a consequence of acute ethanol exposure have been previously implicated in this adaptive response. These genes were functionally tested and robustly correlated with the emergence of alcohol tolerance. However, ways in which we can harness the reversibility of this epigenetic landscape pharmacologically to treat alcohol addiction remain unknown. Recent research supports the noncompetitive NMDA antagonist ketamine as a treatment for depression and addiction. It is hypothesized that exposure to ketamine could be modulating the epigenetic regulation of gene expression in favor of changes that oppose the regulatory outcomes observed after alcohol consumption. Here, we use a combination of behavioral analyses of drug exposure in a Drosophila model system and molecular analyses of gene expression to characterize the genetic, physiological and behavioral responses to alcohol and ketamine. After monitoring fly activity patterns, total sleep of female flies increased after exposure to alcohol while males remained near baseline level. After monitoring female and male flies exposed chronically to two ketamine doses, we found 0.1mg/mL dose of ketamine decreases total sleep of female flies. These results suggest that an attenuated dose of ketamine serves to restore the effect of alcohol on fly sleep. Cluster analysis of genes responding to alcohol and ketamine will help us advance the search for a pharmaco-epigenetic treatment that intercepts the development of alcohol tolerance at the initial stages of the cycle of addiction.

Disclosures: A.M. Padilla: None. **M. Ramírez:** None. **C. Billini:** None. **M. Francia:** None. **J. Agosto:** None. **A. Ghezzi:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.01/BBB10

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA Grant R01 AA024527

Title: Sex differences in intermittent access voluntary alcohol consumption and probabilistic reversal learning tested in protracted withdrawal

Authors: *C. G. AGUIRRE[1], Y. SEGURA[1], S. KOLLI[1], A. STOLYAROVA[1], V. MARTY[2], A. IZQUIERDO[1], I. SPIGELMAN[2]
[1]Psychology, [2]Sch. of Dent., Univ. of California- Los Angeles, Los Angeles, CA

Abstract: Various groups have tested the effect of forced alcohol (ethanol, EtOH) exposure on reversal learning, a widely-used assay of cognitive flexibility. A variety of methods have been implemented for this type of alcohol administration, including intragastric gavage and vapor inhalation, resulting in significant impairments in reversal learning. Although voluntary models of consumption produce lower blood alcohol levels than those induced by forced exposure models (that typically yield tolerance and alcohol dependence), they do allow for individual differences in alcohol consumption and subsequent variability in performance. To our knowledge there has been limited investigation of sex differences in alcohol consumption and their effects on later cognitive flexibility measures. Here, we studied male (n=8) and female (n=8) adult Long Evans rats that underwent 10 weeks of voluntary intermittent EtOH access using a 2-bottle choice (2-BC) procedure. Rats were given access to both water and 10% EtOH for a 24-hour period (3 days/week) and only water on the remaining days. After completing the 2-BC regimen, rats were mildly food restricted to work for food rewards (sugar pellets) in operant conditioning chambers. Rats were then pretrained for probabilistic reversal learning (PRL), which included acclimating to the conditioning chambers, collecting rewards from the magazine, and learning to nosepoke stimuli presented on a touchscreen. The task is designed to assess rats' sensitivity to probabilistic outcomes and their ability to adapt to changes in reward contingencies. In the PRL task, rats chose between two visual stimuli, assigned as the Better (B) or Worse (W) options, rewarded with probability $p_R(B)=0.70$ or $p_R(W)=0.30$, respectively. Thus far, we found a significant within-subject effect of day on EtOH consumption, indicating an escalation of consumption [$F_{(28, 392)}=6.68$, $p<0.0001$], a marginally-significant interaction of sex x day [$F_{(28,392)}= 1.51$, $p=0.05$], and a trend for a significant effect of sex [$F_{(1, 14)}=3.42$, $p=0.09$]. Females reached higher maximum EtOH consumption than males [$t(14)=3.46$, $p=0.004$], and needed

more pretraining sessions to reach criterion to advance to PRL, [t(14)=3.49, p=0.004]. At present, mostly males have advanced to PRL. We plan to correlate EtOH consumption with the number of trials to criterion on PRL. We have also recently found reinforcement uncertainty-induced differential expression of excitatory and inhibitory receptors in basolateral amygdala (BLA), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) assessed via immunohistochemistry. These are similar targets of interest for the present study.

Disclosures: C.G. Aguirre: None. **Y. Segura:** None. **S. Kolli:** None. **A. Stolyarova:** None. **V. Marty:** None. **A. Izquierdo:** None. **I. Spigelman:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.02/BBB11

Topic: G.08. Drugs of Abuse and Addiction

Support: This research was supported by "Instituto de Salud Carlos III" (RETICS, RD12/0028/0019 and RD16/0017/0014), "Plan Nacional Sobre Drogas" (PNSD 2016/016) and "Ministerio de Economía y Competitividad" (FIS, PI14/00438) to JManzanares.

Title: Gender-dependent effects of cannabidiol on ethanol binge drinking in mice

Authors: *J. MANZANARES, A. VIUDEZ-MARTÍNEZ, M. GARCÍA-GUTIÉRREZ
Inst. de Neurociencias, Univ. Miguel Hernandez-Csic, San Juan de Alicante, Spain

Abstract: Binge drinking has become a major public health concern due to its high prevalence in modern societies and the scarce and limited pharmacological options available for its clinical management. In this sense, cannabidiol (CBD) has been recently proposed as a potential therapeutic tool in the treatment of alcohol use disorders (AUD) since its administration reduces ethanol consumption, motivation to drink and ethanol-induced relapse in mice. Furthermore, CBD also protects against the neurodegenerative effects induced by ethanol intoxication; however, its effects on heavy alcohol use patterns, such as binge drinking, were unexplored to date. The aim of the present study was to evaluate the effects of CBD on binge drinking and analyze potential gender-related differences. To this purpose, male and female C57BL/6J mice (n=40/sex) were exposed to 4 cycles of the drinking in the dark procedure (DID), a model of binge drinking. Dose-response effects of CBD (15, 30 and 60 mg/kg; i.p.) on the ethanol intake were tested by acute (day-4 of cycle-3) or repeated administration (day-1 to 4 of cycle-4). Changes in the gene expression of tyrosine hydroxylase (TH) and μ-opioid receptor (Oprm1) in the ventral tegmental area (VTA) and in nucleus accumbens (NAc), respectively, were also analyzed by real time PCR. Females exposed to DID exhibited higher values of ethanol intake

compared to their male counterparts (Two-way RM ANOVA; $P<0.001$). Interestingly, TH and Oprm1 gene expression was also significantly higher in females (Student's t-test; $P<0.05$). Repeated but not acute administration of high doses of CBD (30 and 60 mg/kg) significantly reduced ethanol consumption in males (Two-way RM ANOVA; $P<0.05$). Repeated administration of CBD 60 mg/kg also reduced the relative gene expression of TH and Oprm1 in males (One-way ANOVA; $P<0.05$). Nevertheless, CBD failed to induce any of these effects in females. Considering the high rates of ethanol intake by females, it seems feasible to hypothesize that the differential effects produced by CBD could be related with the differential ethanol consumption between both genders. Further studies evaluating the effects of higher doses of CBD and different administration schedules are needed. Taken together, these findings demonstrate for the first time the potential utility of CBD in the treatment of binge drinking by reducing ethanol consumption in a heavy alcohol use pattern and how gender related differences in binge drinking can affect the treatment outcome.

Disclosures: J. Manzanares: None. **A. Viudez-Martínez:** None. **M. García-Gutiérrez:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.03/BBB12

Topic: G.08. Drugs of Abuse and Addiction

Support: DGAPA-PAPIIT Grant IA205218
DGAPA-PAPIIT Grant IN215218
DGAPA-PAPIIT Grant IN217918

Title: Maternal Separation modifies the circadian rhythm of water intake

Authors: *K. REYES-SANTIAGO[1], L. MOLINA ARCIA[1], M. MENDEZ DIAZ[2], A. E. RUIZ-CONTRERAS[3], O. PROSPERO-GARCIA[4]
[1]Univ. Nacional Autonoma de Mexico, Mexico, Mexico; [2]Univ. Nacional Autonoma de Mexico Facultad de Medicina, Mexico DF, Mexico; [3]Lab. Neurogenomica Cognitiva, Fac. Psicologia, UNAM, D.F., Mexico; [4]UNAM, Mexico, D. F., Mexico

Abstract: Maternal separation (MS) has been implicated in the induction of brain reprogram that negatively impact adult life behaviors. The aim of this work was to determine if MS at early age modifies the endogenous rhythm of water intake and the rhythm of alcohol intake. Male Wistar rats was separated from their mothers during 3h daily from postnatal day (PND) 2 to PND15 (MS), control (NMS) group remained with the mother at all times until the day of weaning, PND21. From PND60, the circadian rhythm of water intake was measured. Two bottles of water were placed in the rats' box during 10 days in light-dark cycle (LDC, 12:12, lights were turned

on at 8:00 a.m.), followed by 2 weeks in continuous darkness. During 2 additional weeks they returned to the LDC. In the following 19 days (LDC) their voluntary consumption of alcohol (1 bottle with 10% v / v of alcohol and the other of water) was evaluated. Results did not show significant differences between MS and NMS subjects in the duration of the endogenous period of water intake. However, differences were found in the endogenous profile of water intake (frequency of activity throughout 24h). In addition, MS spent more days to entrainment than NMS rats. No significant differences were found in the duration of the period during access to alcohol between MS and NMS rats. However, a longer duration of alpha was found during the period of alcohol access both MS and NMS rats. These findings show that MS at early age modifies the circadian rhythm of water intake without affecting the rhythm of alcohol consumption, suggesting that alcohol possesses more strength to synchronize rats' rhythms.

Disclosures: K. Reyes-santiago: None. **L. Molina Arcia:** None. **M. Mendez Diaz:** None. **A.E. Ruiz-Contreras:** None. **O. Prospero-Garcia:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.04/BBB13

Topic: G.08. Drugs of Abuse and Addiction

Title: Effects of ethanol pre-exposure and age on the acquisition and extinction of conditioned taste aversion in C57Bl/6J mice

Authors: J. M. CHOQUETTE, I. K. GALIC, E. M. GRAFELMAN, *S. D. DICKINSON
Psychology and Neurosci. Program, St. Olaf Col., Northfield, MN

Abstract: Adolescents, both human and rodent, consume more alcohol than do adults, a finding believed to result from a combination of a propensity for reward seeking and a decreased sensitivity to the aversive effects of alcohol during adolescence. Previous research from our lab shows that alcohol exposure prior to place conditioning in mice produces tolerance to its aversive motivational effects more quickly in adolescents than adults. In addition, findings from one-trial conditioned taste aversion (CTA) studies indicate decreased aversion in adolescent rats, with higher doses sometimes necessary to produce CTA in adolescent mice and rats relative to adult animals. CTA can develop after pairing a tastant (CS) with an injection of alcohol, and is thought to assess the aversive motivational properties of the drug. In the present study, we combined ethanol pre-exposure with a multiple trial CTA procedure to determine the impact of pre-exposure on both the initial level of ethanol-induced CTA as well as its rate of development. We also investigated age-related differences in the extinction of CTA in animals with or without alcohol pre-exposure. Naive adolescent (PND 21) and adult (PND 56) male C57BL/6J mice received a moderate (2 g/kg) dose of ethanol every other day for four days prior to taste

conditioning. On conditioning days, mice received 1h access to a 1.6 mM saccharin solution, then received a moderately high dose of ethanol (3 g/kg) or an equivalent volume saline injection. The conditioning days were followed by extinction trials, whereby the mice were exposed to the saccharin solution with no injection. All mice who received ethanol-paired saccharin exposure show a significant decrease in saccharin consumption over conditioning days, demonstrating the expected development of conditioned taste aversion. Across conditioning days, adolescent mice who received four ethanol pre-exposures learned the CS-US association more slowly than other groups. Retarded acquisition of conditioned taste aversion in the ethanol pre-exposed adolescents suggests that an interaction between age and pre-exposure produces a tolerance to the aversive effects of ethanol. The rate of extinction did not vary significantly on the basis of age or pre-exposure, though a non-significant effect of age showed adolescents tended to consume more saccharin than adults during later extinction trials. More rapid extinction could indicate weaker learning of the taste aversion, or a relative decrease in the magnitude of the aversion. Future research should be aimed at elucidating the mechanisms underlying these age differences.

Disclosures: J.M. Choquette: None. **I.K. Galic:** None. **E.M. Grafelman:** None. **S.D. Dickinson:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.05/BBB14

Topic: G.08. Drugs of Abuse and Addiction

Support: P60 AA011605, R25 GM089569

Title: Adolescent intermittent ethanol impairs behavioral flexibility in rats

Authors: *G. A. GOMEZ ACOSTA, N. Y. A. SEY, Y.-Y. I. SHIH, C. A. BOETTIGER, D. L. ROBINSON
Bowles Ctr. for Alcohol Studies, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Emerging evidence has shown that patterns of teen drinking, which include binge drinking, produce physiological and behavioral effects to the developing brain that can persist into adulthood. Alcohol use disorder (AUD) is associated with behavioral inflexibility and bias toward rewards. We recently reported that adolescent intermittent ethanol (AIE) exposure promoted inflexible sign-tracking (ST) and reduced flexible goal-tracking (GT) in adult rats, which is consistent with enhanced cue conditioning and reduced behavioral flexibility. The present study includes two experiments, both of which tested AIE effects on flexible behavior. Experiment 1 determined whether AIE similarly impaired action selection in a stimulus-response

(S-R) task using a foraging response. Experiment 2 (partial results) sought to replicate AIE effects in promoting STB and the effects obtained in the Experiment. We hypothesized that AIE will promote inflexible behavior independently of the behavior testes, showing that adolescent exposure to ethanol impairs cognitive functioning and increases an individual's vulnerability to develop an AUD during adulthood. Exp. 1: rats were exposed to ethanol during adolescence (5 g/kg/day, 2 days on/2days off, P25 - 55). In adulthood, they were trained to dig for a food reward that was buried in one of two media and cued with one of two odors. Results: AIE and control rats both learned to discriminate olfactory cues, but AIE rats were less likely to learn to reverse that discrimination on the reversal test day. However, AIE rats were faster to return to the original odor discrimination (a second reversal; $p< 0.05$), suggesting perseverative behavior. Exp. 2: after AIE, animals underwent Pavlovian Conditioned Approach where a light was followed for a delivery of 100µL 20% sucrose. Then, after two weeks of food restriction, rats underwent the S-R foraging task. Results: AIE animals decreased flexible GT (reduced elevation score ($p<0.05$), increase receptacle entry (RE) latencies ($p<0.01$) and decrease RE probability ($p<0.01$). For the digging task, AIE rats were less likely to learn to reverse the initial discrimination on the reversal test day ($p<0.05$). No differences were observed in this cohort for the second reversal. Conclusions: While the study is ongoing, the findings are consistent with previous studies reporting that AIE decreases flexible GT behaviors. Also, these results are in concordance with studies of people presenting with substance abuse disorder, who learned new stimulus-response associations similarly to control subjects, but made more perseverative errors when that stimulus-response was replaced (McKim et al., 2016).

Disclosures: G.A. Gomez Acosta: None. **N.Y.A. Sey:** None. **Y.I. Shih:** None. **C.A. Boettiger:** None. **D.L. Robinson:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.06/CCC1

Topic: G.08. Drugs of Abuse and Addiction

Support: MinCyT
CONICET
SeCyT- UNC

Title: Perinatal lead exposure modifies the locomotor effects of ethanol in *Caenorhabditis elegans*: Role of ethanol metabolism

Authors: *P. A. ALBRECHT[1], A. V. CARRANZA[2], R. DEZA-PONZIO[1], L. E. FERNÁNDEZ-HUBEID[1], L. M. CANCELA[1], R. ASÍS[2], M. ASCHNER[3], M. B. VIRGOLINI[1]
[1]IFEC-CONICET. Depto. de Farmacología, [2]CIBICI-CONICET. Depto. de Bioquímica Clínica,

Fac de C Químicas.Universidad Nacional de Córdoba, Córdoba, Argentina; [3]Dept. of Mol. Pharmacol., Albert Einstein Col. of Med., Bronx, NY

Abstract: Previous studies have demonstrated that developmental lead (Pb) exposure induces higher susceptibility to several responses to ethanol in rats. Caenorhabditis elegans has been used to study the neurobehavioral responses to drugs, including ethanol. Within this context, an acute ethanol exposure induces an initial sensitization and afterward tolerance to its sedative effects on motility. Wild-type (N2) nematodes in the L3 stage were exposed to $Pb(NO3)_2$ 5mg/L during 96 h until their progeny reached the L1 stage. Thereafter, they were washed and transferred to a new plate free of Pb with food for 48 h. The ethanol effects on motility were evaluated in L3 controls and perinatally Pb-exposed worms, 2 h after the ethanol concentration in the agar reached 100, 200 or 400 mM. The average speed of ten worms was registered for 2 min period either 10 min or 30 min after the onset of ethanol exposure to evaluate the initial depressor response that was followed by a recuperation effect characteristic of ethanol effects on motility. The results demonstrate that 200 mM of ethanol was the optimal dose to elicit differences between the control and Pb-exposed groups. In effect, the sedative effects of the drug were observed in the controls opposite to the hyperactivity manifested in the Pb-exposed animals. In addition, the use of a mutant strain that lacks the alcohol dehydrogenase (ADH)-like enzyme which metabolizes ethanol to acetaldehyde prevented the manifestation of these differences. Thus, the enduring hypermotility observed in the Pb group after ethanol exposure suggests a potentiation in the development of tolerance to the sedative effects of ethanol. Furthermore, the acetaldehyde seems to play a critical role in ethanol metabolism in the manifestation of these effects in the Pb-exposed worms

Disclosures: A.V. Carranza: None. **R. Deza-Ponzio:** None. **L.E. Fernández-Hubeid:** None. **L.M. Cancela:** None. **R. Asís:** None. **M. Aschner:** None. **M.B. Virgolini:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.07/CCC2

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA R01 AA024434
NIGMS Center for Nervous System Function COBRE P20 GM103645 (sub # 8278)

Title: Assessing motivational drive to attain ethanol in *Drosophila melanogaster*

Authors: *J. CATALANO[1], N. MEI[2], R. AZANCHI[3], S. SONG[1], T. BLACKWATER[1], F. MAHMUD[1], K. R. KAUN[2]
[2]Neurosci. Grad. Program, [3]Dept. of Neurosci., [1]Brown Univ., Providence, RI

Abstract: Understanding ethanol's complex effects on reward and motivation circuits in the brain is critical for the development of better biologically informed therapies for ethanol abuse and addiction. Recent advances in neurogenetics have highlighted *Drosophila melanogaster* as an exciting model to study the effects of ethanol at the circuit and single neuron levels. However, methods for assessing motivation for drugs like ethanol are lacking in the *Drosophila* field. To address this methodological gap, we have developed a memory assay for investigating the motivational drive for odors and/or vaporizable stimuli like ethanol. Our results suggest that *Drosophila* demonstrate both seeking and avoidance behaviors for ethanol. Further, high content analysis reveals a number of factors that affect the decisions to seek alcohol. Future studies will assess the necessity and sufficiency of specific neuronal circuits in ethanol mediated seeking and avoidance. This experimental paradigm for estimating motivational drive will allow for circuit, single neuron, molecular, and genetic analyses of ethanol's motivational effects. Our results will also help inform similar conserved circuit motifs in mammalian models.

Disclosures: J. Catalano: None. **N. Mei:** None. **R. Azanchi:** None. **S. Song:** None. **T. Blackwater:** None. **F. Mahmud:** None. **K.R. Kaun:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.08/CCC3

Topic: G.08. Drugs of Abuse and Addiction

Title: Day-night variation in ethanol related behaviors in *Drosophila* and mice

Authors: *K. M. CAPRI, M. J. MARONI, M. H. CHASSE, A. V. CUSHMAN, J. A. SEGGIO
Biol. Sci., Bridgewater State Univ., Bridgewater, MA

Abstract: Both acute and chronic ethanol exposure is well known to produce modifications to the biological clock. In turn, mutations to genes that regulate the circadian rhythm also alter ethanol related behaviors and metabolism. Here, we report day-night variation in behavioral outcomes for both *Drosophila* and mice and that acute alcohol exposure may influence those behaviors. For all experiments listed, separate groups of animals were tested for the following behaviors during ZT 6-8 (middle of the day) or ZT 18-20 (middle of the night) while in a 12:12 LD cycle. Male and female flies of wild-type, alcohol dehydrogenase (ADH) nulls, and ADH enhanced mutants were subjected to 500µL of ethanol in a vial to determine their sedation and recovery times for two consecutive days to assess alcohol sensitivity and tolerance respectively. While no differences are found during the first day of ethanol testing, an interaction between time of day and fly strain was found. ADH null strains exhibited longer recovery times during the day compared to at night. ADH null strains during the day had longer recovery times compared to ADH positive strains, but this effect was not observed during the night.

Additionally, ADH positive strains has quicker recovery from acute ethanol during the day than at night. Male Black Swiss mice were either injected with saline or 2 g/kg ethanol and were assayed in the open field, the light-dark (LD) box in bright light and LD box in the dark. Rearing was more prevalent during the day than night for vehicle injected animals, but not ethanol animals. Additionally, ethanol animals during the day had increased distance traveled in the LD box, but there was no difference at night. These results indicate that the time of day may influence behavioral outcomes in commonly used behavioral assays and that ethanol can modulate those behaviors in a circadian manner.

Disclosures: K.M. Capri: None. **M.J. Maroni:** None. **M.H. Chasse:** None. **A.V. Cushman:** None. **J.A. Seggio:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.09/CCC4

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/NIMHD 2G12MD007592
NIH/NIAAA R15AA020996
NIH/NIGMS 2R25GM069621-14.

Title: Effects of social environment on alcohol responses

Authors: *C. M. SIERRA, P. R. SABANDAL, K.-A. HAN
The Univ. of Texas at El Paso, El Paso, TX

Abstract: Alcohol consumption is influenced by social environments. Clinical studies indicate that human subjects experience increased euphoria when drinking alcohol in social gatherings compared to drinking alone. Furthermore, animal studies show that housing either in a group (socially-enriched) or isolation (socially-deprived) alters the amount of alcohol intake and sedation latency. There is, however, limited information on the neurobiological mechanism by which social environments affect alcohol intake and responses. To begin to address this knowledge gap, we utilized the *Drosophila melanogaster* model. *Drosophila* has been extensively studied on alcohol-associated behaviors including sedation, tolerance, changes in locomotor activity, behavioral disinhibition and sensitization. In our study, we subjected wild-type flies to either single or group housing and subsequently exposed them to ethanol. We monitored the flies' initial sensitivity to sedation, tolerance development and a locomotor response profile to ethanol. We found that singly housed males or females were less sensitive to the sedative effect of ethanol compared to group-housed flies. This suggests that social isolation reduces ethanol sensitivity, increasing ethanol intake. This may enhance adaptive changes

relevant to alcohol abuse and addiction in socially-isolated animals or individuals. We are currently investigating the underlying neurobiological mechanism. Findings of this study may have novel implications for social environment-dependent alcohol use or addiction. This work was supported by the NIH grants NIMHD 2G12MD007592, NIAAA R15AA020996 and NIGMS RISE program 2R25GM069621-14.

Disclosures: C.M. Sierra: None. **P.R. Sabandal:** None. **K. Han:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.10/CCC5

Topic: G.08. Drugs of Abuse and Addiction

Support: Grand Valley State University Center for Scholarly and Creative Excellence
Grand Valley State University Ronald E. McNair Scholars Program

Title: CRF_2receptor regulation of anxiety- and depressive-like behavior following protracted withdrawal from ethanol

Authors: L. MARSHALL, F. SANTOME, *G. R. VALDEZ
Dept Psychol, Grand Valley State Univ., Allendale, MI

Abstract: Alcohol withdrawal is often characterized by symptoms of anxiety and depression. These changes can be long-lasting in nature, which contributes to the challenge of the long-term management of alcoholism. The corticotropin-releasing factor (CRF) system is an important mediator in the behavioral changes following alcohol withdrawal. Two genes encoding distinct G-protein coupled CRF receptors have been identified, the CRF_1receptor and the CRF_2receptor. The strategy of utilizing CRF_1receptor antagonists for treating alcoholism has been aggressively pursued but has thus far been unsuccessful. In contrast, relatively little is known regarding the role of CRF_2receptors in regulating the long-term behavioral changes associated with alcohol dependence. The objective of the present study was to examine the ability of the selective CRF_2receptor agonist urocortin 3 (Ucn 3) to reduce anxiety- and depressive-like behaviors following protracted abstinence from ethanol. In the first experiment, male and female Wistar rats were surgically implanted with intracerebroventricular (icv) cannulas and then fed an ethanol or control liquid diet for 4 weeks. After removal of the diet, they were assessed for physical withdrawal signs, and then left undisturbed for 5 weeks. At the end of this withdrawal period, rats where given icv injections of 10 µg of Ucn 3 or vehicle 10 min prior to testing in the elevated plus maze. Results showed that vehicle-treated rats that were fed the ethanol liquid diet spent less time exploring the open arms of the elevated plus maze, an indication of an increased anxiety-like state, which was reversed by injections of Ucn 3. The second experiment examined

depressive-like behavior using the forced swim test. A second group of male and female Wistar rats were implanted with icv cannulas, fed an ethanol or control liquid diet, and assessed for physical withdrawal signs as described. Following a similar 5-week period of abstinence, rats were exposed to a 5-min session of forced swim stress. The following day, rats were given icv injections of 10 µg of Ucn 3 or vehicle 10 min prior to another 5-min forced swim session that was recorded and examined for time spent immobile. Analysis showed that vehicle treated rats that were fed the ethanol liquid diet spent significantly more time immobile, an indication of an increased depressive-like state, compared to ethanol rats injected with Ucn 3. These results support the hypothesis that CRF_2receptor activation may attenuate long-term changes in stress-related behaviors following protracted abstinence from ethanol, and that CRF_2receptors may provide a novel target for the treatment alcohol-related stress.

Disclosures: L. Marshall: None. **F. Santome:** None. **G.R. Valdez:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.11/CCC6

Topic: G.08. Drugs of Abuse and Addiction

Support: PRODEP PTC-550, 511-6/17-8017

Title: Energy drinks and its combination with ethanol, increases anxiety and depression in Wistar rats

Authors: *M. MUNOZ ARENAS[1], D. POBLANO PÁEZ[1], B. B. VÁZQUEZ GONZÁLEZ[1], A. D. DIAZ[2]
[1]Facultad de Ciencias Químicas, BUAP, Puebla, Mexico; [2]Facultad de Ciencias Quimicas, BUAP, Puebla, Mexico

Abstract: The consumption of energy drinks (BE) has increased dramatically in recent years, marketed with the claim that these products provide an energy boost to improve the physical and cognitive performance caused by the ingredients that make them up in the population of adolescents and young adults have become more frequent the consumption of these drinks combined with alcohol to subjectively reduce the effects of alcohol and improve their alertness, however, some researchers and health organizations have expressed concern about the possible health risks associated with the mixture of alcoholic and energy drinks. The objective of this work was to study the behavioral and cellular changes produced by the co-administration of energy drinks and ethanol in Wistar rats. We used 48 male Wistar rats (Rattus norvegicus) of 150 g which were divided into 4 groups: S.S.I. (control), Ethanol, energy drink and energy drink plus ethanol. The administration was carried out daily for a period of 75 days orally. Behavioral tests

were performed before, during and after the administration, which were: tail suspension and open field tests. The co-administration of energy drinks with ethanol causes an anxiogenic state in the study subjects that leads them to increase their motor activity. Finally, rats were gently sacrificed, and we obtained striatum and hippocampus for to meassure the concentration of nitrites (NO2-). We found an increment of nitrites in the subjects administered with the mixture of energy drinks and ethanol. The effects of the consumption of energy drinks combined with ethanol represent a health risk.

Disclosures: M. Munoz Arenas: None. **D. Poblano Páez:** None. **B.B. Vázquez González:** None. **A.D. Diaz:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.12/CCC7

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA T32 AA007474

Title: Role of perineuronal nets in the IfL during fear extinction and reinstatement after AIE

Authors: *K. L. MARQUARDT[1], L. CHANDLER[2]
[1]Neurosciences, Med. Univ. of South Carolina, Charleston, SC; [2]Dept Neurosciences, Med. Univ. S Carolina, Charleston, SC

Abstract: Adolescent alcohol use primes alcohol-cue conditioning systems and reward learning leading individuals who drink during adolescence to be more susceptible to developing a pattern of un-controlled drinking in adulthood. Classically conditioned cue associations can be modeled in rodents with a fear conditioning paradigm, in which a mild foot shock is paired with a tone, the conditioned cue. Extinction learning in which the tone no longer predicts a shock, is mediated by an infralimbic (IfL) cortex and basolateral amygdala circuit. We have previously shown adolescent intermittent ethanol (AIE) exposure slows extinction learning and impairs extinction recall in male rats when tested in adulthood. However, the mechanisms behind this impairment have not been fully explored. Disruption of perineuronal nets (PNN) in the amygdala has been reported to result in a labile fear memory that is susceptible to erasure during extinction learning. In addition, repetitive alcohol consumption in adulthood increases PNN density around parvalbumin positive fast-spiking (FS) interneurons in the frontal cortex. PNNs form preferentially around these FS interneurons and continue to mature well into young adulthood in the prefrontal cortex (PFC), coinciding with maturation of PFC networks. These data lead to our hypothesis that impairment of fear extinction learning and recall in male rats after adolescent alcohol exposure is mediated by aberrant increases in PNN density in the IfL cortex. Beginning

on postnatal day 30, adolescent rats were exposed to five cycles of ethanol vapor chamber exposure. Each two-day cycle consisted of 14-hour vapor chamber exposure, followed by 10-hours out of the chamber, resulting in an average blood ethanol concentration of 250 mg/dl at the end of each cycle. Twenty-four hours, 7 and 26 days following the last cycle of ethanol exposure, PNN intensity in the medial prefrontal cortex (mPFC) was examined utilizing PIPSQUEAK software. Data suggest that AIE increases PNN density in the mPFC, and that this increase persists into adulthood. Furthermore, our data show that fear extinction learning modifies PNN density in the IfL, and that disruption of PNN in the IfL by chondroitinase ABC impacts extinction learning and later extinction retention.

Disclosures: K.L. Marquardt: None. **L. Chandler:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.13/CCC8

Topic: G.08. Drugs of Abuse and Addiction

Title: Reward processing alterations for natural reward in alcohol-preferring (P) rats: Incentive contrast, reward discrimination, and alcohol consumption

Authors: *J. J. MCGRAW[1], R. S. GOLDSMITH[2], H. C. CROMWELL[2]
[1]Psychology, Bowling Green State Univ., Lancaster, NY; [2]Psychology, Bowling Green State Univ., Bowling Green, OH

Abstract: Relative reward effects highlight the impact of reward value shifts on goal-directed behavior. A popular method used to examine relative reward effects is incentive contrast. Positive contrast is an upshift or increase in behavior toward a particular outcome due to an alternative comparison, while negative contrast is the opposite. The ability to compare rewards and utilize value shifts to make advantageous outcome decisions may be disrupted in substance use disorders such as alcohol use disorder (AUD). We examined the natural reward comparison abilities of Sprague-Dawley (SD) and alcohol-preferring (P) rats in an operant task using 12 sucrose solution pairings to determine 1) the impact of food restriction on contrast; 2) potential line differences in contrast before P rat alcohol exposure; 3) alcohol effects on contrast in P rats; and 4) the impact of reward value shifts on P rat alcohol intake. Animals underwent a repeated-measures design consisting of two single outcome blocks separated by a mixed outcome block. Appetitive and consummatory measures were used to assess positive and negative contrast toward single outcomes relative to alternatives presented during mixed blocks. Restricted naïve P rats show generalization and inverse consummatory contrast as well as impaired relative preference and a lack of reward discrimination. Conversely, they show appetitive contrast and discrimination for sucrose outcomes, suggesting that P rats have enhanced reward seeking but

upon consumption abandon their valuation of initial outcomes due to an impaired memory-based reward process which limits contrast and enables them to be hyposensitive to natural reward unlike alcohol. Alcohol had no effect on the absence of contrast in unrestricted P rats. Alcohol intake and preference were altered after incentive contrast tests but due to a lack of contrast, it was unclear whether sucrose upshift or downshift impacted drinking. We conclude that P rats show inherent deficits in reward processing and altered reward comparison abilities which could highlight genetic predispositions in AUD. Food restriction was found to be a key mediator of contrast in SD rats and P rats and analysis of both phases of motivation (appetitive and consummatory) is crucial in examining contrast and reward comparison abilities.

Disclosures: J.J. McGraw: None. **R.S. Goldsmith:** None. **H.C. Cromwell:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.14/CCC9

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA U01AA025932
NIAAA R01AA021505

Title: Modulation of alcohol-seeking behavior by optogenetic induction of corticostriatal LTP in D2-MSNs of transgenic rats

Authors: *A. BINETTE, Y. CHENG, X. WANG, J. WANG
Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Our previous study found that excitation of dopamine D2 receptor-expressing medium spiny neurons (D2-MSNs) in the dorsomedial striatum (DMS) transiently reduced alcohol consumption in mice (Cheng et al., Biological Psychiatry 2017). In this project, we examine whether optogenetic induction of corticostriatal long-term potentiation (LTP) in DMS D2-MSNs alters alcohol-seeking behavior. We used recently developed DRD2-Cre transgenic rats to test this possibility. First, we found that intra-DMS infusion of AAV-DIO-tdTomato led to strong fluorescence expression in DMS neurons that project to the external segment of the globus pallidus, but not in those projecting to the substantia nigra pars reticulata (SNr). In addition, infusion of green beads in the SNr caused green fluorescent labeling of DMS neurons that were not overlapped with tdTomato-positive neurons. These data suggest that Cre is selectively expressed in D2-MSNs. Next, we infused AAV-chronos into the medial prefrontal cortex (mPFC) and AAV-flex-chrimson into the DMS of DRD2-Cre rats and trained the animals to self-administer 20% alcohol in operant chambers. We implanted optical fibers into the DMS, induced corticostriatal LTP by pairing optogenetic mPFC stimulation and optogenetic depolarization of

DMS D2-MSNs, and tested its consequence on operant alcohol-seeking behavior. LTP-induction produced a significant reduction in alcohol consumption which lasted for 10 days. Because depolarization of MSNs can evoke long-term depression (LTD) via endocannabinoid release, we performed a third LTP-induction paired with systemic administration of the endocannabinoid CB1R antagonist AM251. LTP-induction in the presence of AM251 significantly modulated alcohol consumption but not lever presses. Lastly, we performed a devaluation test and found that rats that were sensitive to devaluation showed a greater LTP-induced reduction in lever presses. These data suggest that corticostriatal LTP-induction in D2-MSNs is sufficient to cause a reduction in alcohol consumption.

Disclosures: A. Binette: None. **Y. Cheng:** None. **X. Wang:** None. **J. Wang:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.15/CCC10

Topic: G.08. Drugs of Abuse and Addiction

Support: FAPESP 2013/24986-2

Title: Involvement of the hippocampus in context-induced alcohol-seeking in rats

Authors: *F. C. CRUZ[1], J. M. F. JESUS[1], T. S. YOKOYAMA[1], C. R. ZANIBONI[1], P. PALOMBO[1], S. A. ENGI[1], P. C. BIANCHI[2], R. M. LEÃO[3]
[1]Pharmacol., Univ. Federal de Sao Paulo, Sao Paulo, Brazil; [2]PANT, UNESP - State Univ. of São Paulo, Araraquara, Brazil; [3]ICS, Univ. Federal da Bahia, Salvador, Brazil

Abstract: One of the main problems in the treatment of drug addiction is relapse to drug use after extended period of abstinence. In human addicts and rat models, environmental stimuli associated with previous drug use can provoke relapse to drug seeking. Pre-clinical studies have used the ABA renewal procedure to study context-induced reinstatement of drug seeking. Here, we assessed the role of hippocampus in context-induced reinstatement of alcohol self-administration in rats. Male Long-Evans rats were trained to self-administrate alcohol in context A. Alcohol self-administration was extinguished in a distinct context-Context B. On the test day, animals were re-exposed to the alcohol context A or the extinction context B for 30 min. The reexposure to the ethanol-associated Context A reinstated cocaine seeking and increased expression of Fos in the dorsal hippocampus neurons. To assess a causal role for this brain region, after the extinction phase cannulas were bilaterally implanted into the dorsal hippocampus and on the test day animals received either vehicle or Cobalt Chloride 15 min, prior the contexts exposure. The inhibition of dorsal hippocampus attenuated alcohol seeking in

context A. Our results suggest the participation of the dorsal hippocampus in context-induced alcohol seeking behavior

Disclosures: F.C. Cruz: None. **J.M.F. Jesus:** None. **T.S. Yokoyama:** None. **C.R. Zaniboni:** None. **P. Palombo:** None. **S.A. Engi:** None. **P.C. Bianchi:** None. **R.M. Leão:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.16/CCC11

Topic: G.08. Drugs of Abuse and Addiction

Support: FAPESP 2013/24986-2

Title: The role of the amygdala in context-induced reinstatement of alcohol self-administration in rats

Authors: *R. M. LEÃO[1], L. T. CAMARGO[2], P. PALOMBO[2], P. C. BIANCHI[3], P. E. OLIVEIRA[4], F. C. C. CRUZ, 04023062[5]
[1]Federal Univ. of Bahia - UFBA, Salvador, Brazil; [2]Pharmacol., Univ. of Sao Paulo USP, Sao Paulo, Brazil; [3]PANT, UNESP - State Univ. of São Paulo, Araraquara, Brazil; [4]Univ. Estadual Paulista, Araraquara, Brazil; [5]Pharmacol., Univ. Federal de Sao Paulo, Sao Paulo, Brazil

Abstract: Relapse is the major problem in ethanol addiction treatment. After prolonged withdrawal, drug relapse is often precipitated by acute re-exposure to drug-associated environment. Central and basolateral amygdala nuclei play a key role in learned associative behaviors. Thus, molecular and synaptic changes in neurons of the amygdala could be involved in context-induced relapse behavior. Here, we investigated whether context-induced reinstatement of alcohol seeking is correlated to amygdala activation. For this purpose, Long-Evans rats learned to associate a context (context A) with alcohol reward effects. Subsequently, they were exposed to a different non-drug context (context B) to extinct alcohol seeking behavior. Then, context-induced the reinstatement of alcohol seeking was tested by re-exposing the rats to the alcohol-associated context A. The re-exposure to the context A, but not to the context B, caused reinstatement of alcohol seeking. Fos-expressing neurons were increased in basolateral amygdala (BLA) in both contexts. However, in the central amygdala (CeA) the number of Fos-positive cells was increased only in context B. Cholinergic and GABAergic interneurons were the main types of neurons activated in the amygdala nuclei during the reinstatement of alcohol-seeking. Our data suggest that neuronal activation of distinct amygdala nuclei is involved with extinction and/or reinstatement of alcohol self-administration in rats.

Disclosures: R.M. Leão: None. **L.T. Camargo:** None. **P. Palombo:** None. **P.C. Bianchi:** None. **P.E. Oliveira:** None. **F.C.C. Cruz:** None.

Poster

686. Drugs of Abuse and Addiction: Alcohol: Other Behavioral Effects

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 686.17/CCC12

Topic: G.08. Drugs of Abuse and Addiction

Support: USPHS Grant R00AA021782

Title: Early emotional manifestations of problematic alcohol drinking in rats

Authors: *S. PANDEY, J. R. BARSON
Dept. of Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Severe alcohol use disorder (AUD), resulting from chronic excessive alcohol drinking, is characterized by dysregulated cognitive, emotional, and motivational states which perpetuate aberrant drinking behavior. While these disruptions and their underlying neuropathology have been investigated in animal models of alcohol addiction, it remains unclear whether alterations in behavior and neurobiology also occur in initial stages of the AUD trajectory. Therefore, we evaluated the emotional state of adult, male Long-Evans rats drinking 20% ethanol for 8 weeks under the intermittent-access paradigm, and compared them with that of animals maintained on water and chow only. Based on their intake level, we further grouped the alcohol drinking animals by tertile split as high drinkers (intake > 6.5 g/kg/24hrs) or low drinkers (intake < 4 g/kg/24hrs). When tested immediately prior to daily ethanol access, and 24 hours since their last access, the high drinkers, compared to the low and water drinkers, showed reduced anxiety and greater exploration in otherwise anxiogenic and risky novel environments (elevated plus maze, light-dark box), but reduced exploration in familiar and relatively safer environments (hole board apparatus, home cage) (n = 5-7/group). These findings with the high drinkers may reflect a sensation-seeking and risk-taking phenotype. Notably, we found that behaviors exhibited in an open field prior to the initiation of alcohol access subsequently changed after several weeks of drinking in the alcohol drinkers, but not in the water drinkers, indicating that these phenotypes likely developed as a consequence of alcohol drinking, rather than reflecting a preexisting difference. We conclude that, even in a non-dependence model, repeated excessive alcohol drinking is linked to robust alterations in emotional states and behavior. These early emotional changes in high alcohol drinkers may strengthen the drive to continue drinking at high levels, pushing them towards dependence. We are currently investigating neurobiological alterations that may mediate these emotional changes. Ultimately, identifying similar emotional changes in humans may be useful in preventing susceptible individuals from progressing into the AUD trajectory.

Disclosures: S. Pandey: None. **J.R. Barson:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.01/CCC13

Topic: G.08. Drugs of Abuse and Addiction

Support: EU MedBioinformatics Grant 634143
MINECO SAF2016/75966-R
Retic (ISCIII) RD16/0017/0010

Title: Prenatal and postnatal alcohol exposure alters cocaine reinforcing effects in adult mice

Authors: *L. CANTACORPS[1], S. MONTAGUD-ROMERO[1], M. LUJÁN[1], O. VALVERDE[1,2]
[1]Univ. Pompeu Fabra, Barcelona, Spain; [2]IMIM-Hospital del Mar Res. Inst., Barcelona, Spain

Abstract: Maternal binge alcohol drinking during prenatal and postnatal periods can be deleterious for the fetus since it occurs during key periods of the brain development. It is known that in utero alcohol exposure may lead to a wide range of long-lasting morphological and behavioral deficiencies known as fetal alcohol spectrum disorders (FASD), associated with a higher risk of later developing neuropsychiatric disorders. However, little is known about the long-term consequences on cocaine use and abuse in individuals with FASD. This study aimed to investigate the effects of maternal binge alcohol consumption cocaine reward-related behaviors in adult offspring. Pregnant C57BL/6 female mice were exposed to an experimental protocol of binge alcohol drinking (drinking-in-the-dark test) throughout gestation up to weaning. Then, male offspring were left undisturbed until they reached adulthood and were tested for cocaine-induced rewarding responses (conditioned place preference, behavioral sensitization and operant self-administration). Results show that prenatal and postnatal alcohol exposure enhances the preference for the lowest dose of cocaine-paired chamber in the conditioned place preference test (5 and 10 mg/kg). Furthermore, early alcohol exposed mice display an attenuated behavioral sensitization to cocaine at both doses tested (7.5 and 10 mg/kg), but greater attenuation was observed with the lowest dose. In addition, cocaine self-administration acquisition was higher in alcohol-exposed mice. Our findings demonstrate that maternal binge-like alcohol consumption during gestation and lactation enhances the sensitivity to the conditioned rewarding effects of cocaine in offspring mice. Together, these data suggest that prenatal and postnatal alcohol exposure may underlie an enhanced susceptibility of alcohol-exposed offspring to develop substance abuse disorder later in adulthood.

Disclosures: L. Cantacorps: None. **S. Montagud-Romero:** None. **M. Luján:** None. **O. Valverde:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.02/CCC14

Topic: G.08. Drugs of Abuse and Addiction

Support: MJ Murdock Charitable Trust

Title: Requirement of brain ghrelin signaling in the acquisition of cocaine reward

Authors: D. P. DUNN, J. M. R. BASTACKY, S. ABTAHI, E. HOWELL, *P. J. CURRIE
Dept. Psychology, Reed Col., Portland, OR

Abstract: We have previously shown that microinjection of ghrelin into the ventral tegmental area (VTA) potentiates cocaine-induced conditioned place preference (CPP). Other work now indicates that systemic administration of JMV2959, a ghrelin 1a receptor antagonist, attenuates both cocaine and amphetamine-induced CPP. To further investigate the role of mesolimbic ghrelin in the modulation of cocaine reward, the present study examined the ability of ghrelin administration into either the VTA or nucleus accumbens (NAc) to potentiate the acquisition of cocaine-induced CPP. Additionally, we investigated the impact of JMV2959 pretreatment in order to evaluate the potential attenuation of ghrelin's action on cocaine-induced CPP resulting from the inhibition of ghrelin 1a signaling. Adult male Sprague-Dawley rats were allowed access to either side of the CPP apparatus to establish baseline chamber preferences. The rats were then restricted to either their non-preferred or preferred side over the course of conditioning which lasted for a total of 8 consecutive days. On days in which rats were restricted to their non-preferred side, systemic cocaine (0.5-5.0 mg/kg IP) was injected and followed by either ghrelin (300 pmol), or JMV2959 (10 μg) paired with ghrelin (300 pmol), into either the VTA or NAc immediately prior to the conditioning trial. On alternate days rats were treated with vehicle both IP and centrally and placed into what was initially determined to be their preferred side. CPP was calculated as the difference in the percentage of total time spent in the treatment-paired compartment during the post-conditioning session and the pre-conditioning session. Our results indicated that both VTA and NAc ghrelin potentiated the acquisition of cocaine-induced CPP and that this effect was attenuated by JMV2959. Overall, these findings provide further evidence that central ghrelin 1a signaling is indeed involved in mediating the rewarding effects of psychostimulant compounds.

Disclosures: D.P. Dunn: None. **J.M.R. Bastacky:** None. **S. Abtahi:** None. **E. Howell:** None. **P.J. Currie:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.03/DDD1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA R01-DA031734

Title: Continuous social stress: Individual effects on cocaine self-administration in mice

Authors: *D. T. ARENA[1], K. A. MICZEK[2]
[2]Psychology, [1]Tufts Univ., Medford, MA

Abstract: Vulnerability to the effects of social stress can vary greatly across individuals. In C57BL/6J adult male mice, brief episodes of social defeat stress consistently *escalate* cocaine-self administration and heighten reinstatement after periods of abstinence. By contrast, continuous exposure to experiences of social defeat often result in the emergence of depression-like characteristics. Anhedonic behavior as measured by reduced sucrose preference, social interactions and *suppressed* responding for cocaine is hypothesized to be the result of continuous social defeat. The present experiments aimed to delineate the critical parameters of social stress in mice as they engender divergent patterns of intravenous cocaine self-administration. Separate groups of male C57Bl/6J mice were studied after 10 days of either intermittent or continuous social defeat stress, or no social stress. Following a 10-day period, mice were examined for social interaction and sucrose preference. The mice were then implanted with permanently indwelling IV catheters either in the jugular or femoral vein, acquired and maintained cocaine self-administration under a fixed ratio 1 schedule of reinforcement (0.3 mg/kg/inf) and then tested at several doses (0.1, 0.03, 0.01, 0.003, 0.001). Mice that underwent continuous stress reliably interacted less with a social stimulus animal, while intermittent social stress experience had no effect. Intermittent social defeat engendered a consistent increase in cocaine self-administration behavior at the training dose and a significantly sensitized response as measured by increased taking at lower doses. Two divergent phenotypes emerged in subgroups of continuously stressed mice: significantly escalated or significantly suppressed self-administration across all doses tested. These data provide evidence for contrasting effects of, not only intermittent versus continuous social stress, but also continuous social stress alone on subsequent cocaine intake. We seek to characterize the animals that self-administer cocaine either at high or low modes in terms of behavioral and neurochemical profile.

Disclosures: D.T. Arena: None. **K.A. Miczek:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.04/DDD2

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA033641
NIH Grant DA028874

Title: A role for Cdkn1a in mediating the epigenetic inheritance of cocaine resistance in male offspring

Authors: *S. E. SWINFORD-JACKSON[1], B. FANT[1], M. E. WIMMER[2], M. C. KNOUSE[1], A. S. THOMAS[1], R. C. PIERCE[1]
[1]Dept. of Psychiatry, Univ. of Pennsylvania, Philadelphia, PA; [2]Dept. of Psychology, Temple Univ., Philadelphia, PA

Abstract: Preclinical evidence indicates parental exposure to drugs of abuse alters behavior and physiology of offspring. We previously demonstrated that when male rats self-administered cocaine, their male, but not female, progeny displayed reduced cocaine self-administration. The heritable epigenetic marks in sperm, including DNA methylation and histone post-translational modifications, that mediate differences in the reinforcing efficacy of cocaine in offspring are not fully understood. Recent evidence suggests DNA methylation is a stable epigenetic modification which may be involved in transgenerational epigenetic inheritance. Indeed, we identified 272 differentially methylated regions between the sperm of cocaine- and saline-experienced sires using a reduced representation bisulfite sequencing approach. Two hypomethylated promoter regions were upstream of the cyclin-dependent kinase inhibitor 1a (*Cdkn1a*) gene. A potential role for Cdkn1a in modulating cocaine reward is bolstered by a recent report which showed enhanced cocaine conditioned place preference in a global *Cdkn1a* knockout mouse (Scholpa et al., 2016). Here, we tested the hypotheses that Cdkn1a hypomethylation in the sperm of cocaine-experienced sires vs. saline-experienced sires is associated with higher Cdkn1a expression in male offspring, and overexpression of nucleus accumbens Cdkn1a will reduce cocaine self-administration in naïve rats. Expression of *Cdkn1a* mRNA in the nucleus accumbens was upregulated in cocaine- vs. saline-sired male offspring; there was no difference in female offspring. DNA methylation at the *Cdkn1a* promoter in the nucleus accumbens was not altered in cocaine-sired vs. saline-sired male offspring, suggesting that an alternate mechanism, rather than DNA hypomethylation, drives overexpression of Cdkn1a in the accumbens of male offspring. Experiments to functionally validate the impact of Cdkn1a overexpression on cocaine self-administration using a virally-mediated gene delivery in the nucleus accumbens of naïve rats are ongoing. Our results suggest Cdkn1a hypomethylation in sperm is a novel epigenetic mechanism

by which cocaine experience produces transgenerational effects, and Cdkn1a levels in the nucleus accumbens may mediate the reinforcing efficacy of cocaine.

Disclosures: S.E. Swinford-Jackson: None. **B. Fant:** None. **M.E. Wimmer:** None. **M.C. Knouse:** None. **A.S. Thomas:** None. **R.C. Pierce:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.05/DDD3

Topic: G.08. Drugs of Abuse and Addiction

Support: NHMRC project grant (#1102012)
NHMRC CDF: #1045643
Rebecca Cooper Equipment Grant "Understanding Cannabinoid Abuse in Schizophrenia"

Title: Altered cocaine reward, but not reinforcement, in a neuregulin 1 mouse model of schizophrenia

Authors: *R. CHESWORTH[1], T. KARL[2,3,4]
[1]Sch. of Med., Campbelltown North, Australia; [2]Sch. of Med., Western Sydney Univ., Sydney, Australia; [3]Neurosci. Res. Australia, Sydney, Australia; [4]Sch. of Med. Sci., Univ. of NSW, Sydney, Australia

Abstract: Substance abuse is highly prevalent in schizophrenia patients, worsening symptoms, increasing hospitalisation rates, and reducing the effectiveness of antipsychotic medication. It is unclear why substance abuse is so common in schizophrenia. Limited evidence suggests genetic predisposition for schizophrenia may make patients more susceptible in developing drug addiction. Elevated drug abuse propensity can be examined using mouse models of genetic risk for schizophrenia. The *neuregulin 1* transmembrane domain heterozygous (*Nrg1* TM HET) mouse shows face, construct and predictive validity for schizophrenia, and displays altered behavioural and neural responses to the major psychoactive component of cannabis. However, the rewarding and reinforcing properties of abused drugs have not been assessed in these mice. Thus, we examined the rewarding and reinforcing properties of cocaine in male *Nrg1* TM HET mice, as cocaine is abused in schizophrenia at a rate 10x times higher than in control populations. Cocaine reward (10 and 20mg/kg i.p.) was assessed in conditioned place preference, where the pairing of a drug with a neutral context can produce a preference for the drug-paired context (n=8-10/genotype and dose). At 10mg/kg cocaine, WT mice showed a strong preference whereas *Nrg1* TM HET mice did not develop a preference for the cocaine-paired context. However, at 20mg/kg cocaine, WT mice showed a neutral preference, and *Nrg1* TM HET mice showed a

strong preference for the cocaine-paired context. This suggests higher cocaine doses, at the maximal end of the dose response curve for WT mice, continue to induce reward in *Nrg1* TM HET mice. The reinforcing properties of cocaine were examined using intravenous self-administration (n=8-10/genotype). Reinforced responding for cocaine (0.5mg/kg/infusion) was examined with a fixed ratio 1 schedule of reinforcement (FR1), and motivation for cocaine was tested with a progressive ratio schedule of reinforcement (PR) at the same dose. *Nrg1* TM HET and WT mice made a similar number of cocaine infusions during FR1 training. There were no genotype differences in the motivation to self-administer cocaine. This suggests the reinforcing nature of cocaine at the dose chosen was similar in *Nrg1* TM HET and WT mice. The data presented suggest *Nrg1* TM mutation can increase the rewarding nature of higher dose cocaine. This finding provides first evidence for a potential genetic link between schizophrenia and cocaine abuse, and may help explain elevated abuse rates of this drug in patients. If higher doses are required to induce reward, this can lead to stronger cocaine-induced neural adaptations and a higher propensity for addiction.

Disclosures: R. Chesworth: None. **T. Karl:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.06/DDD4

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant 2R01DA024716-06

Title: Estradiol mediates the development of motivational features of an addicted phenotype in female rats

Authors: *A. BAKHTI-SUROOSH[1], T. NESIL[2], W. J. LYNCH[3]
[1]Psychiatry and Neurobehavioral Sci., [2]Psychiatry & Neurobio. Sci., [3]Psychiatry and Med., Univ. of Virginia, Charlottesville, VA

Abstract: Women develop cocaine addiction faster after initial use compared to men. Animal models reveal a similar vulnerability in females, with estradiol implicated in the development of the features of addiction. However, most of this research has been conducted in ovariectomized females with and without estradiol replacement. In order to focus more directly on the contribution of estradiol, without manipulating all other ovarian hormones, we tested the effects of the estrogen receptor (ER) antagonist tamoxifen in intact females. We hypothesized that tamoxifen would block the development of addiction, as defined by an enhanced motivation for the drug, use despite negative consequences, and relapse vulnerability. Intact female rats were treated chronically (5-days/week) with tamoxifen (1.0 mg/kg; n=12) or vehicle (oil; n=17). A no

treatment group was also included to control for the effects of vehicle (n=9). Motivation for cocaine (0.5 mg/kg/inf) was assessed at baseline (following acquisition) and then following extended access (ExA) self-administration (SA; 24-hr; 4 discrete trials/hr; 1.5 mg/kg/inf; 10 days) and 14-days of abstinence, using a progressive ratio schedule (PR). Use despite negative consequences was then examined on a stable PR baseline by adding histamine, which induces an aversive response (2 and 4 mg/kg), to cocaine solutions. Relapse vulnerability was examined following abstinence in separate groups of rats under an extinction/cue-induced reinstatement procedure (n=8/group). As expected, tamoxifen prevented the development of an enhanced motivation for cocaine. While both the vehicle and no treatment groups showed an enhanced motivation for cocaine, the increase was higher in the no treatment versus the vehicle group (39 versus 18%), indicating that the oil itself reduced vulnerability. In contrast to effects on motivation, tamoxifen did not seem to prevent the development of relapse vulnerability, and actually increased extinction responding, or use despite negative consequences, as all groups showed only moderate decreases in PR SA after histamine was added. These results suggest that while estradiol mediates the development of motivational aspects of addiction, it may not be critical to the development of other key features, including use despite negative consequences and relapse vulnerability. However, given that tamoxifen also tended to decrease intake and inactive responding during ExA SA, and markedly reduced body weight, presumably via an estrogenic mechanism, it is possible some of our findings were mediated independent of tamoxifen's anti-estrogenic effects. Future research is needed to address this possibility.

Disclosures: A. Bakhti-Suroosh: None. **T. Nesil:** None. **W.J. Lynch:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.07/DDD5

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA037844

Title: Intermittent access to cocaine enhances drug-directed motivation without altering response to food stimuli

Authors: *C. P. KING, J. A. TRIPI, H. A. PEARSON, P. MEYER
Psychology, Univ. at Buffalo, Buffalo, NY

Abstract: Patterns of drug-taking behavior are important in determining drug-directed motivation. Specifically, "intermittent-access" schedules of cocaine reinforcement result in "spiking" levels of brain cocaine levels, and lead to enhanced motivation for the drug, compared to "continuous access" schedules in which drug is freely available (Zimmer et al. 2012). In

addition, the tendency to approach food-associated stimuli ("sign-tracking") is associated with sensitivity to the motivational properties of cocaine (Saunders et al. 2010). Thus, to test whether intermittent cocaine access alters the response to food cues, we measured Pavlovian Conditioned Approach (PavCA) behaviors before and after rats had intermittent access to cocaine.
Experiment 1: We measured CS-directed (sign-tracking) and US location-directed ("goal-tracking") behaviors in Sprague-Dawley rats (n = 22) over three days of PavCA. Next, rats were trained to self-administer cocaine continuously for either 2-hours, 6 hours, intermittently in twelve 5 minute bins over 6-hours ("intermittent-access") or saline over 2 hours. Subjects were then assessed for drug-directed motivation using a threshold probe procedure, in which responses needed to maintain preferred level of drug intake are slowly increased. Subjects were then again tested in PavCA for changes in cue-directed approach, followed by a cue-seeking procedure where subjects respond for the cocaine-paired cue. We found that intermittent access rats showed greater motivation to work for cocaine and cocaine cues compared to the continuous access groups and saline controls. However, we found no changes in approach to a food cue following self-administration, suggesting the effects of intermittent access are specific to drug conditioning.
Experiment 2: In a separate cohort, we measured rats' response to an auditory food CS, which elicited goal-tracking in all animals (n = 18). We found that food conditioning was unaffected by drug schedule, again indicating that newly learned approach behaviors to non-drug stimuli are not altered by these different schedules of self-administration.
The results of these two studies indicate that, although intermittent access schedules can potentiate drug-directed behavior, these behavioral effects do not translate to non-drug stimuli. Therefore, it is suggested that neuroadaptations in response to intermittent self-administration are specific to drug domains, and may not produce global changes in stimulus-driven behavior.

Disclosures: C.P. King: None. **J.A. Tripi:** None. **H.A. Pearson:** None. **P. Meyer:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.08/DDD6

Topic: G.08. Drugs of Abuse and Addiction

Support: FONCyT PICT 2015 1622 (Argentina)
SECyT UNC 212/16 (Argentina)
CONICET (Argentina)

Title: Chronic restraint stress and vulnerability to develop cocaine self-administration: Dysregulation of glutamate homeostasis in nucleus accumbens core

Authors: *L. M. CANCELA[1], M. P. AVALOS[1], A. S. GUZMAN[1], D. RIGONI[1], C. GARCIA-KELLER[2], F. A. BOLLATI[1]
[1]IFEC-CONICET. Dept Pharm. Sch. of Chem Sci. Nat Univ. of Cordoba, Cordoba, Argentina; [2]Neurosci., Med. Univ. of South Caroline, Charleston, SC

Abstract: Clinical evidence proved a facilitatory influence of stress on the development of substance use disorders. However, the mechanisms underpinning the comorbidity between stress and drug abuse have not been completely elucidated. Data from our lab demonstrated that chronic exposure to restraint stress engenders long-lasting neuroadaptations in Nucleus Accumbens (NAc), the major limbic-motor integration area, which resulted in sensitized response to cocaine (Esparza et al., 2012). We also showed that an acute exposure to restraint stress revealed that an enduring locomotor sensitization to cocaine is paralleled by an increase in dopamine (DA) within the NAc core, but not the shell. Our lab also found that rats pre-exposed to acute stress showed an increase in basal levels of glutamate (GLU) in the NAc core as measured by the no-net-flux method (Garcia-Keller et al., 2013). A relationship between altered basal GLU and the glutamate transporter GLT-1 levels was proposed to underlie the facilitation of cocaine self-administration (SA) following acute pre-exposure to stress (García-Keller et al., 2016). The present study attempts to determine the long-term effects of chronic pre-exposure to restraint stress on extracellular levels of DA and GLU in NAc, its impact on locomotor activity and drug SA behavior, and the levels of GLT-1 in the neuropathology of cocaine abuse induced by stress. Male Sprague Dawley rats (300-350g) were exposed to chronic restraint stress (2 h x day for 7 days), and 2 weeks later the following experiments were carried out: 1) Determination of DA and GLU extracellular levels in NAc core and shell after saline or cocaine (15 mg/kg i.p.), by microdialysis followed by High-Performance Liquid Chromatography coupled with electrochemical detection, 2) Basal GLU levels in NAc core by the no-net-flux method, 3) GLT-1 protein expression in NAc (preferentially core) by Western blotting, 4) Cocaine SA behavior and locomotor activity following saline or cocaine challenge injection. This study points out that chronic restraint stress induced a dopaminergic sensitization within NAc core, but not shell, after acute cocaine. Also, an increase of basal extracellular levels of GLU in core was observed following chronic stress, which is consistent with the decreased expression of GLT-1 in NAc. We propose that the chronic restraint stress-induced dysregulation of glutamate homeostasis is related to its influence on the development of cross-sensitization to motor stimulant effect of cocaine and the facilitation of the acquisition of cocaine SA behavior.

Disclosures: L.M. Cancela: None. **M.P. Avalos:** None. **A.S. Guzman:** None. **D. Rigoni:** None. **C. Garcia-Keller:** None. **F.A. Bollati:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.09/DDD7

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA043799

Title: Large-scale phenotyping of addiction-like behaviors in outbred rats identifies three types of individuals: Resistant, vulnerable, and prone to compulsive-like cocaine use

Authors: *O. GEORGE[1], M. BRENNAN[2], D. CONLISK[2], L. MATURIN[2], L. SOLBERG WOODS[3], A. A. PALMER[4], G. DE GUGLIELMO[2]
[1]Dept. of Neurosci., Scripps Resch Inst., La Jolla, CA; [2]The Scripps Res. Inst., La Jolla, CA; [3]Wake Forest Univ., Winston-Salem, NC; [4]Psychiatry, UCSD, La Jolla, CA

Abstract: Identifying the mechanisms that underlie the greater vulnerability to develop compulsive cocaine use represents a major goal for understanding the genetic risk factors for cocaine use disorder and facilitating the identification of novel druggable targets. We performed a large-scale phenotyping study of the escalation of cocaine self-administration in heterogeneous stock (HS) rats, a unique outbred strain of rats that is characterized by high genetic variability that has been developed to mimic genetic variability in humans. Male and female rats were trained to self-administer cocaine (0.5 mg/kg/inf) in 10 daily 2-h sessions (acquisition phase) and 14 daily 6-h sessions (escalation phase). The animals were also screened for compulsive cocaine use using a progressive-ratio schedule of reinforcement and responding despite adverse consequences (contingent footshocks). To minimize cohort-specific effects, we used three large cohorts (n = 46 each) and normalized the level of responding within sex and cohorts using Z-scores. To take advantage of the three behaviors that are related to compulsive intake and further identify individual differences in compulsive cocaine use, we computed an Addiction Index by averaging normalized responding (Z-scores) for the three behavioral tests. The results showed very high individual variability between subjects that allowed us to identify two different populations of rats: vulnerable (80%) and resistant (20%) to compulsive cocaine use. Further screening of the three factors that characterized the Addiction Index allowed us to identify rats with mild *vs*. severe levels of addiction-like behaviors and a subpopulation of rats with compulsive-like responding. The identification of such individual variability will likely facilitate the detection of gene variants that are associated with vulnerable *vs.* resistant individuals. The results of these studies have the potential to have a sustained impact on the field of addiction because they will identify novel druggable targets, provide a comprehensive analysis of compulsive cocaine use in both males and females, and provide a unique data/tissue repository that will facilitate follow-up and replication studies.

Disclosures: M. Brennan: None. **D. Conlisk:** None. **L. Maturin:** None. **L. Solberg Woods:** None. **A.A. Palmer:** None. **G. de Guglielmo:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.10/DDD8

Topic: G.08. Drugs of Abuse and Addiction

Support: DA011064

Title: FDA-approved 5-$HT_{1B/1D}$ receptor agonist, zolmitriptan, decreases cocaine self-administration in male and female rats

Authors: *R. GARCIA, D. CHARMCHI, A. COTTER, J. BONADONNA, J. L. NEISEWANDER
Arizona State Univ., Tempe, AZ

Abstract: Zolmitriptan is a 5-$HT_{1B/1D}$ receptor agonist that is used clinically to treat migraine headaches. We previously found that zolmitriptan decreases methamphetamine self-administration in male rats. Here we examined if zolmitriptan produces similar effects on cocaine (0.075 & 0.75 mg/kg) and sucrose (45 mg) self-administration in male and female rats. Sprague-Dawley male and free-cycling female rats were tested for the effects of zolmitriptan (0, 3.0, 5.6, & 10 mg/kg, SC) on cocaine and sucrose reinforcement rates on a fixed ratio 5 schedule of reinforcement. In male rats, 5.6 mg/kg of zolmitriptan decreased intake of 0.075 mg/kg cocaine and all doses of zolmitriptan decreased intake of 0.75 mg/kg cocaine. In female rats, 5.6 and 10 mg/kg of zolmitriptan decreased intake of 0.075 mg/kg cocaine and 10 mg/kg of zolmitriptan decreased intake for 0.75 mg/kg cocaine. These same doses of zolmitriptan did not affect sucrose reinforcement rates. The cocaine doses are on the ascending and descending limbs of the dose-effect curve, respectively, suggesting that zolmitriptan decreases cocaine reinforcement in both males and female rats. These findings suggest that zolmitriptan may have clinical efficacy as a treatment for psychostimulant use disorders.

Disclosures: R. Garcia: None. **D. Charmchi:** None. **A. Cotter:** None. **J. Bonadonna:** None. **J.L. Neisewander:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.11/DDD9

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA023957

Title: A novel dopamine d3-receptor antagonist MC250041 reduces cocaine and sucrose self administration

Authors: *S. M. DOYLE[1,2], J. BONADONNA[2], A. ADAMS[2], J. HESTERMAN[2], A. VANNAN[2], R. LUEDTKE[3], R. H. MACH[4], B. E. BLASS[5], P.-J. CHEN[6], K. KORZEKWA[6], M. YE[6], J. NEISEWANDER[2]
[2]Sch. of Life Sci., [1]Arizona State Univ., Tempe, AZ; [3]Hlth. Sci. Ctr., Univ. of North Texas, Fort Worth, TX; [4]Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA; [5]Sch. of Pharm., [6]Tempe Univ., Philadelphia, PA

Abstract: Dopamine D3 receptors (D3Rs) are a potential target for developing therapeutic compounds for psychostimulant addiction. Preclinical research has shown that D3R-selective antagonists and partial agonists attenuate measures of motivation for cocaine; however, obstacles for advancing D3R drugs for clinical trials are the bioavailability and/or short half-life of existing compounds. We have synthesized a novel phenylpiperazine, MC250041, that has an elimination half-life > 15 h and is > 1000-fold selective for D3Rs relative to D2Rs. In this study, we tested the effects of MC250041 (MC) on locomotor activity (N=12) and cocaine self-administration (N=10) using male Sprague-Dawley rats. Rats performed an operant lever press response on a multiple variable interval 60-second schedule with altering, 30-min components of cocaine (0.75 mg/kg, i.v.) and sucrose (45 mg) reinforcement. Once rats showed stable reinforcement rates, we tested the rats for MC effects on intake of the reinforcers at doses of 0.0, 3.0, 5.6, and 10.0 mg/kg (i.p.). We also examined the effects of 5.6 mg/kg MC on locomotor activity induced by 15 mg/kg (i.p.) cocaine. The highest dose of MC reduced the number of cocaine reinforcers obtained without altering sucrose reinforcement. MC potentiated cocaine-induced hyperactivity. The results suggest that MC may be useful in treating cocaine dependence. Future studies are planned for testing MC effects in female rats and for testing MC effects under a progressive ratio schedule of reinforcement to study cocaine motivation more robustly.

Disclosures: S.M. Doyle: None. **J. Bonadonna:** None. **A. Adams:** None. **J. Hesterman:** None. **A. Vannan:** None. **R. Luedtke:** None. **R.H. Mach:** None. **B.E. Blass:** None. **P. Chen:** None. **K. Korzekwa:** None. **M. Ye:** None. **J. Neisewander:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.12/DDD10

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant R01DA038613

Title: Transcriptional adaptations in the ventral pallidum following cocaine self-administration

Authors: *M. ENGELN[1], R. CHANDRA[1], H. QADIR[1], R. HERMAN[2], H. NAM[1], M. E. FOX[1], S. L. COLE[1], M. LOBO[1]
[1]Anat. and Neurobio., Univ. of Maryland Baltimore, Baltimore, MD; [2]Univ. of Maryland, Col. Park, Baltimore, MD

Abstract: Growing evidence suggests that the ventral pallidum (VP) is critical for drug intake and seeking behavior. Receiving dense projections from the nucleus accumbens as well as dopamine inputs from the midbrain, the VP plays a central role in the control of motivated behaviors. Repeated exposure to cocaine is known to alter VP neuronal firing and neurotransmission. Surprisingly, there is limited information on the molecular adaptations occurring in VP neurons following cocaine intake. To provide insight into cocaine-induced transcriptional alterations we performed RNA-Seq on VP of mice that underwent 10 days of cocaine self-administration (0.5mg/kg/infusion) followed by twenty-four hours of abstinence. We observed differential gene expression in 363 genes between animals that self-administered cocaine and saline controls. Among them, the expression of the transcription factor Nr4a1 showed a robust increase. Further, we observed an increase in the Nr4a1 transcriptional target, Plk2, a molecule important for synaptic and structural plasticity. We are currently using fluorescent *in situ* hybridization to determine which VP projection neuron population displays increased Nr4a1 and Plk2 levels after cocaine self-administration. This includes VP- ventral tegmental area, VP-lateral habenula, VP-mediodorsal thalamus, or VP-nucleus accumbens projection neuron populations. Additionally, we are using adenoassociated virus (AAV) overexpression and CRISPR knockdown manipulation of Nr4a1 and Plk2 to interrogate the role of these molecules in VP neuron subtypes during cocaine self-administration and seeking. Altogether, our work can provide crucial information into the molecular substrates occurring in VP neuron subtypes that underlies cocaine self-administration and relapse-like behavior.

Disclosures: M. Engeln: None. **R. Chandra:** None. **H. Qadir:** None. **R. Herman:** None. **H. Nam:** None. **M.E. Fox:** None. **S.L. Cole:** None. **M. Lobo:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.13/DDD11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIHRO1DA038613

Title: Cocaine-induced histone methylation on Egr3 and Nab2 promoters

Authors: *R. CHANDRA[1], B. B. EVANS[2], M. MCGLINCY[2], A. CHOW[2], K. K. COVER[3], M. ENGELN[1], M. K. LOBO[4]
[1]Anat. and Neurobio., Univ. of Maryland Baltimore, Baltimore, MD; [2]Anat. and Neurobio., Univ. of Maryland, Baltimore, Baltimore, MD; [4]Anat. and Neurobio., [3]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The nucleus accumbens (NAc) is a critical brain region, which mediates motivation for drugs of abuse. The NAc is composed of two types of medium spiny neurons (MSNs), which are differentiated by their enrichment of dopamine D1 vs. D2 receptors. We previously demonstrated that the transcription factor, Egr3, is upregulated in D1-MSNs and down-regulated in D2-MSNs after repeated cocaine exposure. It is postulated that Egr3 regulates its co-repressor, Nab2, and they both act together as a feedback mechanism to repress Egr3 transcription. Consistent with this, we observe a reduction of Nab2 in D1-MSNs and an increase of Nab2 in D2-MSNs after repeated cocaine exposure. Interestingly Egr3 also targets many histone methyltransferase and demethylase enzymes. Our previous work demonstrates that Egr3 transcriptionally regulates a histone lysine methylation enzyme in NAc after repeated cocaine exposure and we are currently investigating Egr3 binding on promoters of histone demethylase enzymes including lysine specific histone demethylase 1A, KDM1A, under these same conditions. In parallel we have examined mRNA levels of KDM1A in NAc D1-MSNs and D2-MSNs after repeated cocaine. Similar to Egr3, we observe an enrichment of KDM1A mRNA in D1-MSNs and a reduction in D2-MSNs in the cocaine group compared to the saline control group. We are also examining KDM1A binding and associated histone methylation marks at Egr3 and Nab2 promoters after repeated cocaine exposure. Using chromatin immunoprecipitation (ChIP) we observe altered KDM1A binding, as well as altered H3K4me3 and H3K9me2 on Egr3 and Nab2 promoters in NAc in the cocaine group compared to saline controls. Overall our studies are providing new information into the effects of cocaine on histone demethylation and its potential regulation of Egr3 and Nab2 transcription in MSN subtypes.

Disclosures: R. Chandra: None. **B.B. Evans:** None. **M. McGlincy:** None. **A. Chow:** None. **K.K. Cover:** None. **M. Engeln:** None. **M.K. Lobo:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.14/DDD12

Topic: G.08. Drugs of Abuse and Addiction

Support: P50 DA15369 (JFM)
R01 DA033579 (JFM)
F31 DA039709 (SMB)
F31 DA041021 (BMS)

Title: Chemogenetic inhibition of prelimbic cortical output to paraventricular nucleus of the thalamus prevents anxiety-related behaviors and attenuates cocaine seeking

Authors: *G. GIANNOTTI, S. M. BARRY, B. M. SIEMSEN, J. PETERS, R. A. REICHARD, T. C. JHOU, J. F. MCGINTY
Med. Univ. of South Carolina, Charleston, SC

Abstract: A major clinical issue in addiction is the high rate of relapse even after prolonged abstinence. Our lab has shown that a single infusion of brain-derived neurotrophic factor (BDNF) into the prelimbic (PL) cortex immediately after the last cocaine self-administration session attenuates reinstatement of cocaine-seeking. To dissect the contribution of different cortical efferents to BDNF-mediated attenuation of relapse, we used a combinatorial viral approach to selectively express hM4Di DREADD or mCherry in PL cortical neurons projecting to nucleus accumbens (NAc) core or posterior paraventricular nucleus of the thalamus (pPVT). Male rats were trained to self-administer cocaine for 14 consecutive days. Immediately after the last cocaine self-administration, all rats received an injection CNO (10 mg/kg, I.P.) followed by an infusion into PL cortex of PBS or BDNF 30 min later. Rats then underwent 6 days of abstinence followed by a post-abstinence test under extinction conditions, extinction training to criterion and a cue-induced reinstatement test. As expected, Infusion of BDNF in the mCherry-expressing rats attenuates cocaine seeking. However, activation of hM4Di DREADD in PL->NAc core pathway blocked the BDNF-mediated attenuation of relapse but had no effect on subsequent drug-seeking. Interestingly, inhibition of PL->pPVT, a brain region linked to stress and anxiety, blocked subsequent cocaine-seeking. Moreover, 2h after the last cocaine self-administration session we found that Fos-IR was increased in anxiety-related brain regions, suggesting that early withdrawal may engage anxiety-related structures that support subsequent relapse. To test whether the pPVT is mediating anxiety-related behaviors, rats were tested in the elevated zero maze 2h after the last cocaine self-administration session. We found that activation of hM4Di DREADD in PL->PVT pathway attenuates anxiety-related behaviors compared to mCherry expressing animals. To strengthen the hypothesis that pPVT contributes to the aversive effect of cocaine after its acute rewarding effects disappear, we investigated whether inhibition of pPVT with GABA receptor agonists, baclofen/muscimol, would block avoidance conditioning in a classic operant runway task. As expected, over the sessions PBS-infused rats showed a progressive increase in the run time and number of reversals. However, infusion of bac/mus into pPVT 5 min after the rats reached the goal box after each session blocked the development of conditioned avoidance. These data demonstrate that inhibition of PL->pPVT pathway or pPVT itself prevents anxiety-like behaviors that ultimately contribute to cocaine-seeking.

Disclosures: G. Giannotti: None. **S.M. Barry:** None. **B.M. Siemsen:** None. **J. Peters:** None. **R.A. Reichard:** None. **T.C. Jhou:** None. **J.F. McGinty:** None.

Poster

687. Drugs of Abuse and Addiction: Cocaine Reinforcement

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 687.15/DP12/DDD13

Topic: G.08. Drugs of Abuse and Addiction

Support: RO1 DA033479
F31 DA041021

Title: Biphasic effect of abstinence from cocaine self administration on structural plasticity and AMPA receptor expression in prelimbic cortical neurons projecting to the nucleus accumbens core

Authors: *B. M. SIEMSEN, G. GIANNOTTI, J. A. MCFADDIN, M. D. SCOFIELD, J. F. MCGINTY
Med. Univ. of South Carolina, Charleston, SC

Abstract: Cocaine-induced alterations in dendritic spine morphology in the prelimbic (PrL) cortex and nucleus accumbens (NAc) core are implicated in relapse after abstinence. During early withdrawal from cocaine self-administration (SA) in rats, there is profound dephosphorylation of several markers of glutamatergic transmission including ERK2, GluN2A/B-containing NMDA receptors, as well as CREB in PrL cortex. A single intra-PrL infusion of BDNF normalizes the phospho-protein disturbances during early withdrawal, as well as glutamate release in the NAc core, suppressing relapse. However, one week of abstinence from cocaine SA augments PKA activity, elevating GluA1 and CREB phosphorylation in the PrL cortex. Intra-PrL infusion of the PKA inhibitor, Rp-cAMPs, normalizes the hyper-phosphorylation of CREB and GluA1, suppressing relapse. Because these adaptations have been shown to be associated with altered dendritic spine morphology, we hypothesized that PrL-NAc core neurons would show reduced dendritic spine head diameter and density during early withdrawal, with the opposite occurring after one week of abstinence. Male Sprague-Dawley rats (*N*=32) received an intra-NAc core CAV2-Cre microinjection followed by intra-PrL AAV5-hSyn-DIO-mCherry to label PrL-NAc core neurons, followed by intravenous catheters. Rats underwent 12-14 days of cocaine SA or yoked saline and were perfused either 1) two hours or 2) one week after the final SA session. Coronal sections containing the PrL cortex were immunoprocessed for mCherry and the AMPA receptor subunits GluA1/2, as well as the activity markers pCREB and Fos. High-resolution confocal microscopy was used to image distal apical tuft spine segments of layer V PrL-NAc core neurons. Z-stacks were deconvolved (Huygens) and were 3D reconstructed in Imaris. Experiments were performed individually for GluA1 and GluA2 at both timepoints, and spine data were pooled between experiments. Results showed that cocaine SA decreased Fos immunoreactivity in PrL-NAc neuronal nuclei as well as spine head

diameter, and GluA2 immunoreactivity in putative mushroom-type spines, during early withdrawal, indicating suppressed PrL-NAc core activity at this timepoint. However, after one week of abstinence, dendritic spine density was decreased but spine head diameter and GluA1/2 immunoreactivity in putative mushroom spines were increased in PrL-NAc core neurons, suggesting augmented PrL-NAc core glutamate transmission. Experiments are ongoing to examine pCREB immunoreactivity in PrL-NAc core neurons during early withdrawal and after one week of abstinence.

Disclosures: B.M. Siemsen: None. **G. Giannotti:** None. **J.A. McFaddin:** None. **M.D. Scofield:** None. **J.F. McGinty:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.01/DDD14

Topic: H.01. Animal Cognition and Behavior

Title: Parallel but independent hierarchies of temporal and reward integration across cortex

Authors: *M. MORADI SPITMAAN[1], H. SEO[3], D. LEE[4], A. SOLTANI[2]
[1]Psychological and Brain Sci., [2]Psychological & Brain Sci., Dartmouth Col., Hanover, NH; [3]Psychiatry, Yale Univ. Sch. of Med., New Haven, CT; [4]Neurosci., Yale Sch. of Med., New Haven, CT

Abstract: To uncover principles of cortical computations, previous studies have independently estimated time constants related to intrinsic fluctuations of neural activity and reward feedback in multiple cortical areas. One study reported a hierarchy of intrinsic timescales across cortex (Murray et al., 2014), whereas another identified a power-law distribution of timescales for reward-related neural activity (Bernacchia et al., 2011). These studies, however, used two very different methods for estimating timescales without apparent connections between the results. Importantly, the relationship between the timescales and the task selectivity of individual neurons has not been examined. Here, we developed a general method to simultaneously estimate intrinsic and reward-memory timescales of neural activity observed during a virtual competitive game in the prefrontal (ACC, dlPFC, and dmPFC) and posterial parietal cortex (LIP) of rhesus monkeys, along with the selectivity for task-relevant information. First, we found that our method can replicate previous findings on the hierarchy of intrinsic timescales and a power-law distribution of reward-memory timescales. We also observed a hierarchy for reward-memory timescales that mirrors the hierarchy of intrinsic timescales across the same cortical areas. Second, we examined both intrinsic and reward-memory timescales for neurons with different types of selectivity (choice, reward, and their interaction) and found that the hierarchy of intrinsic timescales was preserved for neurons with different types of selectivity. In contrast,

reward-memory hierarchy was not consistent for different types of neurons and was not present in purely choice-selective neurons. Finally, we did not find any systematic relationship between intrinsic and reward-memory timescales of individual neurons in any cortical areas. Overall, our results reveal a hierarchy for integration of reward signals similar to that for intrinsic timescales when they are estimated simultaneously along with neural selectivity for task-relevant information. Nevertheless, the observed hierarchies of intrinsic and reward-memory timescales were independent, and thus must be generated through different mechanisms.

Disclosures: M. Moradi Spitmaan: None. **H. Seo:** None. **D. Lee:** None. **A. Soltani:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.02/DDD15

Topic: H.01. Animal Cognition and Behavior

Title: A novel paradigm for studying causal inference and temporal credit assignment in nonhuman primates

Authors: *S. K. MURRAY[1], D. LEE[2], H. SEO[3]
[1]Interdepartmental Neurosci. Program, [2]Neurosci., [3]Psychiatry, Yale Sch. of Med., New Haven, CT

Abstract: Previous research has demonstrated that humans and other animals can continually update expected outcomes, or values, of alternative actions based on reward prediction errors. However, in natural environments, causally linked events are often separated in time and by other intervening, but unrelated, events. Furthermore, actions and their outcomes often occur in variable and complex sequences. In such cases, causal inference based on an accurate model of the environment is necessary to update the value of the causative action with the corresponding outcomes appropriately. This problem of linking a particular outcome to its causative action is often referred to as the temporal credit assignment problem. Despite the importance of causal inference and its necessity for solving the temporal credit assignment problem, little is known about the underlying brain mechanisms. As a first step towards understanding how different regions of the primate prefrontal cortex contribute to achieving this complex function, we developed a novel behavioral paradigm. We trained a rhesus monkey to learn the values of multiple actions by iteratively making choices among three alternative peripheral targets. Feedback for the choice on each trial was temporally delayed and delivered after another choice in the subsequent trial. Therefore, the feedback at the end of a given trial was not causally related to the choice in that trial, but rather to the choice made in the previous trial. In order to properly associate action and outcome to inform subsequent choices, the animal must rely on a causal model in which feedback is delayed by one trial. Using a logistic regression model, we found

that animal's choice was determined conjointly by the past choice and its delayed feedback (t-test for regression coefficient, $p<0.001$). By contrast, the conjoint influence of the past choice and causally unrelated immediate feedback was not significant (t-test, $p=0.29$), suggesting that the animal updated the values of different actions based the correct causal model of the task. This result shows that our experimental paradigm provides a new tool necessary to study the neural mechanisms underlying causal inference and resolution of the temporal credit assignment problem.

Disclosures: S.K. Murray: None. **D. Lee:** None. **H. Seo:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.03/DDD16

Topic: H.01. Animal Cognition and Behavior

Support: Gruber Foundation
NIH Grant MH 108629
R01MH112746

Title: Resetting the integrator in perceptual decision-making is reflected in FEF activity

Authors: *M. SHINN[1], H. SEO[2], D. EHRLICH[1], D. LEE[3], J. D. MURRAY[2]
[1]Yale Univ., New Haven, CT; [2]Psychiatry, [3]Neurosci., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Multiple studies have observed a pause or dip in the neuronal activity recorded from the primate frontal eye field (FEF) and lateral intraparietal area (LIP) immediately after the onset of a saccade target. This has been hypothesized to reflect the resetting of information accumulation. Here, we sought to determine whether such a dip in neural activity can be induced by quantitative and more subtle changes in an ongoing sensory stimulus that requires a resetting of evidence accumulation. Two rhesus monkeys were trained to perform a two-alternative forced-choice color-discrimination task, while their saccade reaction times (RT) and single-neuron activity in the FEF were measured. In each trial, the animal was required to determine the majority color in a square consisting of blue and green pixels which were rearranged at 20Hz. The ratio of between green and blue pixels (coherence) for this discriminative stimulus (DS) varied randomly across trials. In addition, DS was preceded by a prestimulus (PS) consisting of equal numbers of green and blue pixels that lasted for 0, 400 or 800ms. Animals were allowed to shift their gaze any time after the onset of the DS and were rewarded only when they chose the target with the same color as the majority of the pixels in the DS. The maximum coherence was set so that the transition from PS to DS was easily noticeable. We found that during the trials with long PS, the frequency of saccades decreased with coherence during an interval between

100 and 200ms after DS onset. This could be accounted for by a drift-diffusion model modified to include the resetting of the evidence integration that was more likely to occur with increasing DS coherence. Consistent with this behavioral model, we found that the FEF activity was reduced approximately 100 ms after the onset of DS, and the size of this dip in FEF activity increased with DS coherence. Although a similar dip in the FEF activity was seen immediately after PS onset, its size was not substantially related to the coherence of DS presented without PS (0ms PS). These results support the idea that the dip in FEF activity is associated with resetting of the integrator during perceptual decision-making, and suggest that the resetting of the integrator reflects the detection of a change in the sensory input.

Disclosures: M. Shinn: None. **H. Seo:** None. **D. Ehrlich:** None. **D. Lee:** None. **J.D. Murray:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.04/DDD17

Topic: H.01. Animal Cognition and Behavior

Support: NSF GRFP to LA

Title: Behavioral mechanisms of reward signaling in the medial and orbital prefrontal cortices

Authors: *L. M. AMARANTE[1], M. S. CAETANO[2], M. LAUBACH[1]
[1]American Univ., Washington, DC; [2]Univ. Federal Do ABC, Santo Andre, Brazil

Abstract: Neuronal activity in the medial prefrontal cortex [mPFC] is synchronized to reward consumption and encodes reward value (Horst and Laubach, 2013; Amarante et al., 2017). Here, we examined several behavioral mechanisms underlying mPFC reward signaling, and also made parallel recordings in the orbital prefrontal cortex [OFC] to assess mPFC-OFC interactions during reward consumption. Rats were trained to perform the Shifting Values Licking Task [SVLT] (Parent et al., 2015) and were subsequently implanted with multi-electrode arrays in the mPFC (prelimbic and adjacent medial agranular areas) and the OFC (lateral orbital and agranular insular areas). Recordings were made in three modified versions of the SVLT: (1) contextual coding was assessed in sessions with reward values (16% and 4% concentration liquid sucrose) held constant over blocks of trials or randomly interleaved across trials; (2) relative value coding was assessed in sessions with three levels of reward, presented in alternating pairs (4% vs 2% sucrose or 4% vs 8% sucrose) over the blocks of trials; and (3) shifts in fluid volume (25 vs 10 ul reward per pump activation), as opposed to shifts in sucrose concentration, were presented in alternating blocks across the session. Spectral analysis of LFPs revealed that lick-entrained activity was coherent across areas, with strong directional influences of the rostral mPFC over

the caudal mPFC and OFC. LFPs in both cortical areas encoded contextual information: e.g. the strength of entrainment to the lick cycle was enhanced when reward values were blocked as compared to when values were randomly interleaved (encoding context, not content). LFPs in both areas also encoded relative value: e.g. stronger entrainment to licking for 4% sucrose when it was presented in alternation with 2% sucrose compared to alternation with 8% sucrose. Finally, LFPs in both mPFC and OFC encoded shifts in fluid volume in a similar way to shifts in sucrose concentration, suggesting that differences in the palatability and magnitude of liquid rewards are similarly encoded in these cortical areas. Together, our studies suggest that neuronal activity in the mPFC exerts top-down influences over the OFC to mediate value-guided control over consummatory actions.

Disclosures: L.M. Amarante: None. **M.S. Caetano:** None. **M. Laubach:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.05/DDD18

Topic: H.01. Animal Cognition and Behavior

Title: Divergence across the rostral-to-caudal axis of the mPFC in the motivational control of behavior

Authors: *H. C. GOLDBACH, T. K. SWANSON, M. LAUBACH
American Univ., Washington, DC

Abstract: Recent studies from our laboratory have established that the medial prefrontal cortex [mPFC] is crucial for the expression of incentive value when rats consume liquid sucrose rewards (Parent et al. 2015). Neuronal recordings in the mPFC further reveal modulations of spike activity and field potential when rats initiate reward consumption that encode differences in reward magnitude (Amarante et al. 2017). These findings were obtained using an operant task based on classic incentive contrast procedures (Flaherty 1982). Here, we used two other types of behavioral tasks to determine if the mPFC is involved in the motivational control of reward consumption. First, rats were tested in a Progressive Ratio Licking Task [PRLT] (Sclafani & Ackroff 2003), in which they had to persistently lick to receive liquid sucrose rewards. The number of required licks increased by 1 after each reward. This design can be used to assess whether reinforcer efficacy depends on a given brain region. Rats were trained to perform the task until they had stable breakpoints before being implanted with guide cannula for delivering muscimol (1μg/μL in 0.5μL) to the mPFC. Cannula were implanted across the rostral-to-caudal axis of the mPFC, targeting the rostral medial orbital and caudal prelimbic areas. Rats with rostral mPFC inactivations (4.2-4.7mm AP) showed reduced rates of performance, and showed changes in microstructural measures of licking, engaging in very brief licking bouts. Rats with

caudal mPFC inactivations (3.2-3.7mm AP) performed the task at a faster pace (reminiscent of Horst and Laubach 2009; 2012) and prolonged their licking bouts. Breakpoints were not affected by inactivations of the mPFC, with the exception of two rats that had cannula implanted in the rostral pole. Second, a different cohort of rats was tested in an operant task in which they nosepoked to produce access to sucrose from an opposing reward port. Similar to results from the PRLT, rostral inactivations led to slower pace and increased collection latencies and caudal inactivations led to faster pace and reduced collection latencies. Together, these studies suggest that while the mPFC is necessary for the expression of incentive value (Parent et al. 2015), there is heterogeneity across the rostral-caudal axis of the mPFC for other measures of motivation, such as response latencies and breakpoints.

Disclosures: H.C. Goldbach: None. **T.K. Swanson:** None. **M. Laubach:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.06/DDD19

Topic: H.01. Animal Cognition and Behavior

Title: Strategic factors in the two-armed bandit task: Computational model, validation in rodents, and role of mPFC

Authors: *T. K. SWANSON[1], H. C. GOLDBACH[2], F. Z. FERNANDEZ[2], B. B. AVERBECK[3], M. LAUBACH[2]
[1]Biol., [2]American Univ., Washington, DC; [3]NIMH/NIH, Bethesda, MD

Abstract: Two-armed bandit tasks (TAB; aka probabilistic reversal learning) are used to assess the neural basis of cognitive flexibility. In these tasks, reversals in reward probabilities over options follow either a performance-based criterion or are blocked over trials, independent of performance. The consequences of this difference in task design are not clear. To address this issue, we developed a normative model of the TAB task, based on win-stay/lose-shift strategies. The model revealed a dominant role of lose-shift behavior (negative feedback) in determining the number of reversals in the performance-based design and of win-stay behavior (positive feedback) in determining choice accuracy in both designs. A reinforcement learning algorithm found evidence for learning around the first reversal in each session, and stable values for alpha and beta thereafter. We validated the model by training rats to perform a spatial TAB task, using training procedures based on recent primate studies (Costa et al. 2015). We found that rats can rapidly be trained to perform the TAB task, even with reward probabilities of 70% and 30% across choice options. Crucially, and in contrast to published studies, rats were trained with deterministic outcomes before experiencing probabilistic outcomes. Using this method, our animals performed well above the choice accuracies and reversals per session that have been

reported in the literature (e.g. Bari et al. 2010; Dalton et al. 2016). When presented with probabilistic (80%-vs-20%) outcomes in a one-hour session (>200 trials), our animals performed with choice accuracies of >70% and made >20 reversals when tested with a performance-based criterion (8 consecutive "correct" choices) and with choice accuracies of >70% when tested with blocked reversals (30 trials per block). Reversible inactivations of the medial prefrontal cortex (mPFC) impaired TAB performance. Infusions of muscimol (5 ng/ul) led to reduced task engagement, reduced choice accuracy, and, in some cases, spontaneous alternation. Together, our studies establish a rodent spatial TAB task that has a clear computational basis, behavioral performance on par with studies in primates, and depends on the mPFC.

Disclosures: T.K. Swanson: None. **H.C. Goldbach:** None. **F.Z. Fernandez:** None. **B.B. Averbeck:** None. **M. Laubach:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.07/DDD20

Topic: H.01. Animal Cognition and Behavior

Support: R01 DA034021 (RMC)
K99 DA042934 (EAW)

Title: Prelimbic-accumbal pathway encoding during learning predicts and is causally linked to behavioral flexibility

Authors: *E. A. WEST, M. NIEDRINGHAUS, R. M. CARELLI
Dept. of Psychology and Neurosci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Animals depend on the ability to modify their behavior to achieve specific outcomes, i.e., behavioral flexibility. The prelimbic cortex (PrL) and nucleus accumbens (NAc) core are necessary for reinforcer devaluation, a test of behavioral flexibility. Previously, we have shown that the degree of encoding in the core predicts the ability of rats to shift behavior later (West and Carelli 2016). Here, we aimed to determine if PrL input is linked to both NAc core cue-encoding and behavioral flexibility. Specifically, male Long-Evans rats (n=21) rats were presented with two distinct cues as conditioned stimuli (CS+; one predicting a sugar pellet and one predicting a food pellet) and two cues that did not predict a reward (CS-); 10 trials each. We recorded neural activity in the PrL and NAc core while rats underwent pavlovian conditioning (10 daily sessions). After 10 sessions, rats were given a devaluation procedure to induce a conditioned taste aversion (LiCl, i.p., 0.3 M; 10 ml/kg) to the sugar pellets. Rats were then tested on the same pavlovian conditioning task (under extinction) to evaluate their ability to avoid CS+ associated with the devalued outcome. Rats spent significantly less time in the food cup during the CS+

associated with the devalued outcome (10.7% +/- 1.4%) compared to the CS+ that predicted the nondevalued outcome (15.2% +/- 1.5%). Recordings of PrL neurons during pavlovian conditioning revealed distinct populations that were excited or inhibited during cue presentations (classified as "phasic"). The change in the number of neurons that were classified as "excited" to the cue from day 1 to day 10 of learning predicted how well rats flexibly changed behavior during testing (R^2= 0.47, p <0.05; measured as a Devaluation Index; DI, West and Carelli 2016). There was no correlation in the change in neurons that were classified as "inhibited" to the cue (R^2= 0.15, p >0.1). In addition, the change in PrL-NAc coherence from Day 1 to Day 10 of learning at the Gamma50 and Gamma80 frequency band predicted how flexible the rats performed during testing (R^2= 0.59, p <0.05 and R^2= 0.82, p <0.05, respectively). This suggests that synchronized high gamma activity between PrL and NAc core during learning is linked to behavioral flexibility in this task. In support, we found that optically inhibiting the PrL-NAc pathway during pavlovian conditioning (during the cue presentations) impaired behavioral flexibility (control, n=6, DI= 0.27 +/- 0.04); halo, n=6, DI=-0.08 +/- 0.13), p<.05), indicating that this pathway is required during cue-outcome acquisition to allow for flexible behavior.

Disclosures: E.A. West: None. **M. Niedringhaus:** None. **R.M. Carelli:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.08/DDD21

Topic: H.01. Animal Cognition and Behavior

Support: R01 DA034021 (RMC)
T32 DA007244 (MLN)

Title: Effects of prior cocaine exposure on delay-based decision making and prelimbic cortical activity

Authors: *M. L. NGBOKOLI, T. M. MOSCHAK, R. M. CARELLI
Psychology and Neurosci., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Individuals suffering from a substance use disorder often show higher rates of impulsive behavior (Coffey et al., Exp Clin Psychopharm, 2003), including an inability to delay gratification (known as delay discounting). Delay discounting relies upon the ability to discriminate both different reward magnitudes as well as different delays to reward, and work has begun to independently investigate the effects of drugs of abuse on magnitude and delay sensitivity. Our lab recently found that abstinence from cocaine self-administration impairs magnitude discrimination and abolishes dopamine encoding of food reward in the nucleus accumbens (NAc) shell (Saddoris et al., Neuropsychopharm, 2017). However, little work has

investigated the neurocircuitry underlying cocaine's effects on delay-based decision making. While the NAc shell appears important in magnitude processing, the NAc core seems to play a stronger role in the processing of delay. Further, the prelimbic cortex (PrL), which projects to the NAc core, exhibits neuroadaptations following cocaine abstinence (West et al., Eur J Neurosci, 2014) and is implicated in delay discounting (Churchwell et al., Behav Neurosci, 2009). Here, we investigated the effects of cocaine self-administration history and abstinence on delay-based decision making and PrL activity using electrophysiological methods. Adult, male Sprague Dawley rats were trained to self-administer cocaine (n=7; 0.33 mg/inf, 2 h per session) or water (to a receptacle) with yoked intravenous saline (n=6) during 14 daily sessions, followed by 30 days of experimenter-imposed abstinence. Rats were then trained to press levers associated with discrete cue lights in a delay task consisting of three trial types. On forced delay trials, a cue light predicted the opportunity (5 s later) to press a lever for a delayed reward (4 s delay). On forced immediate trials, another cue light predicted the opportunity to press a different lever for an immediate reward. During free choice trials, both cue lights and levers were presented, and rats could freely choose either option. Preliminary data indicate that animals with a history of cocaine were faster to press the lever regardless of trial type compared to their saline counterparts, but there was no effect of prior cocaine on free choice behavior. Preliminary results also suggest a correlation trend between PrL firing rate and reaction time ($r = 0.7296$, $p = 0.064$); additional analyses are ongoing. For comparative purposes, we are also examining the effects of prior cocaine experience on uncued delay-based decision making and PrL firing following cocaine history and abstinence.

Disclosures: M.L. Ngbokoli: None. **T.M. Moschak:** None. **R.M. Carelli:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.09/DDD22

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA037229

Title: Integration of value across dimensions in ventromedial prefrontal cortex

Authors: G. LOCONTE[1], H. AZAB[3], M. WANG[4], *B. Y. HAYDEN[2]
[1]Univ. of Minnesota, Minneapolis, MN; [2]Univ. of Minnesota, Saint Paul, MN; [4]Brain and Cognitive Sci., [3]Univ. of Rochester, Rochester, NY

Abstract: In the natural world, the value of a course of action can depend on multiple parameters that can vary independently. In these multi-attribute decisions, value computation requires the on-line integration of the values of each attribute. At the neural level, value

integration can be distinguished from multiplexed responding by a positive correlation between the firing rate tuning functions of variables that influence value in the same way. Here we examine the integration properties of three important value-related brain regions, ventromedial prefrontal cortex (vmPFC, Area 14), pregenual cingulate cortex (pgACC, Area 32), and ventral striatum (VS) in rhesus macaques. We used a two-alternative forced-choice task with staggered option representation while recording from each area. Options differed along the dimension of stakes (two possible juice sizes for winning) and probability (100 values), and all rewards were juice aliquots. Stakes and probability were chosen randomly and independently for each offer on each trial. We found that both vmPFC and VS integrated the two dimensions but that pgACC multiplexed them (i.e. did not integrate to compute value). Moreover, we found that although values were integrated in vmPFC and VS, they were not fully integrated. That is, responses in these regions reflect a partially completed integration process, suggesting that later regions likely complete the process. These results challenge the idea that either vmPFC or VS serves as the endpoint of a value computation process. Moreover, given the integrated value signals observed in human vmPFC, they endorse the hypothesis that Area 14, not area 32, is the macaque homologue of human vmPFC.

Disclosures: G. LoConte: None. **H. Azab:** None. **M. Wang:** None. **B.Y. Hayden:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.10/DDD23

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 DA038106

Title: Cocaine exposure sharpens ventral striatum's encoding of variables in a gambling task

Authors: *P. MEHTA[1], B. J. SLEEZER[2], B. Y. HAYDEN[3]
[1]St Paul, MN; [2]Neurobio. and Behavior, Cornell Univ., Ithaca, NY; [3]Univ. of Minnesota, Saint Paul, MN

Abstract: The ventral striatum (VS) has been implicated as an important component of reward circuits in the brain, active during activities such as substance abuse and gambling. The interaction between substance abuse and encoding of neuroeconomic factors such as risk and reward is relevant both to learning about how substance use can impact human decision making, as well as to understanding how altering VS neurotransmitter levels alters its spike activity patterns. Here, we examine the neural encoding of task variables in rhesus macaque (*Macaca mulatta)* ventral striatum as they perform a gambling task, with and without daily cocaine exposure. Monkeys were presented two successive gamble offers represented as colored bars that

indicated both the size of the reward and the probability of receiving it if that option were selected. The monkeys were then allowed to make a choice between the two offers, which resulted in either reward delivery or lack thereof contingent upon the reward probability. We compared monkeys' behavioral performance and VS neural activity while they performed the task clean, to while they performed the task during a period of days where they received daily self-administered doses of cocaine. Behaviorally, we found that monkeys demonstrated a modest increase in accuracy during cocaine exposure, (selecting the option with the higher expected value of the two). We hypothesize that this increase in accuracy may be due to sharper encoding of the task variables in VS. During offer presentation, more neurons encode the size of the reward during cocaine exposure. Furthermore, the difference in firing rates between different reward sizes is greater in the cocaine condition. Cocaine exposure also brings about an overall increase in signal-to-noise ratio of firing rates: the standard deviation of normalized firing rates over the 2 second period during which offers are being viewed is increased during cocaine exposure. Finally, during cocaine exposure, there is an increased correlation between reward encoding and probability encoding, indicating that cells are encoding these two variables more similarly. These results suggest cocaine exposure heightens the sensitivity of VS in terms of encoding variables relevant to reward-motivated task performance.

Disclosures: P. Mehta: None. **B.J. Sleezer:** None. **B.Y. Hayden:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.11/DDD24

Topic: H.01. Animal Cognition and Behavior

Support: NSF CAREER Award BCS1253576
NIH R01 DA038615

Title: Economic decision-making in freely moving monkeys performing a delay-based foraging task

Authors: *T. CASH-PADGETT, B. Y. HAYDEN
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Decision-making behavior, especially in foraging-based paradigms, may differ with the degree of overlap between an experiment and behaviors that were selected for in an animal's natural environment. Studies of decision-making in nonhuman primates have largely relied on saccade-based tasks, however, and there is still relatively sparse data on value-based decisions in freely moving animals. We examine economic choice behavior in a room-sized environment as rhesus macaques make wait/skip decisions on the basis of wait time required to receive reward.

The length of time is signaled on an LED screen, and is only visible when the subjects are in proximity to the feeder. This behavioral paradigm is known as the 'Restaurant Row', and has been previously used to study economic decision-making and regret in rodents. When a subject approaches a feeder and views the delay, it enters the 'offer zone', and when a subject holds down a lever in order to count down the delay, it enters the 'wait' zone', thereby yielding two distinct economic decisions that must be made. While delays vary pseudorandomly during a session, rewards are consistent within a session for each feeder, and session times are a set duration. We find that subjects consistently accept offered rewards from a full range of delays, but are more willing to wait when a shorter delay is signaled. Thresholds for deciding to wait vary on the basis of the subjective value of rewards obtained from a given feeder. The behavioral results from this experimental paradigm are consistent with foraging-based models of choice behavior, but also suggest differences in attitudes towards risk from those previously observed in saccade-based decision-making tasks.

Disclosures: T. Cash-Padgett: None. **B.Y. Hayden:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.12/EEE1

Topic: H.01. Animal Cognition and Behavior

Support: 31371029
31571121
15JC1400104
16JC1400100

Title: Independent coding of reward and perceptual salience in the lateral intraparietal area in value-based decisions

Authors: *Z. WU[1], X. CAI[2], A. CHEN[1]
[1]East China Normal Univ., Shanghai City, China; [2]NYU Shanghai, Shanghai, China

Abstract: It is generally believed that when making economic choices, we first assign values to available options then compare them to generate a decision. The lateral intraparietal area (LIP) has been considered a candiate neural substrate where action values associated with saccade are represented and compared. This proposal is largely based on the finding that in monkeys making value-based decisions, activity of an LIP neuron correlates with the reward expected from saccade into the neuron's response field. In the mean time, LIP neurons receives projection from many visual areas and they respond with higher firing rate to visual stimuli of higher luminance, suggesting that their activity reflect not only reward but also perceptual salience. To understand

the detailed representation of these two streams of information and its implication for value-based decisions, we trained monkeys to perform a two-alternative choice task in which we independently manipulated reward and perceptual salience by varying the volume of juice and the relative luminance associated with each target. We discovered that the animal's choice was driven by reward but not perceptual salience. We thus recorded from LIP to investigate how its activity may contribute to such choice behavior.
We have recorded 177 neurons in LIP of which 48% (86/177) showed significant spatial tuning. Preliminary results show that the early activity of 39.5% (34/86) neurons was significantly modulated by the amount of reward presented on the neuorns' preferred hemifield. We also discovered that luminance level of the visual stimuli significantly affected the activity of 29.1% (25/86) LIP neurons indicating that the visual responses in LIP are modulated by perceptual salience as well. However, the same neurons tend to be modulated by either reward or salience but not both (only 8 out of 86 neurons responded to both reward and salience). Furthermore, we divided the neurons into anterior (36/86) and posterior (50/86) groups according to the recording coordinates along the anterior-posterior axis relative to the interaural line. Compared to the posterior group, anterior LIP neurons are more sensitive to reward ($p<0.05$, non-paired t test) but less sensitive to luminance ($p<0.01$, non-paired t test) and the reverse is also true.
In summary, both reward and perceptual salience are represented by LIP but are encoded by separate population of neurons. Furthermore, there seems to be a gradient in response to reward and perceptual salience along the anterior-posterior axis of LIP.

Disclosures: Z. Wu: None. **X. Cai:** None. **A. Chen:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.13/EEE2

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 DA038615

Title: Transient tuning of dACC neurons with mixed selectivity in a naturalistic pursuit task

Authors: *J. TU, S. M. YOO, B. Y. HAYDEN
Ctr. for Magnetic Resonance Res., Univ. of Minnesota, Minneapolis, MN

Abstract: The real-world foraging decision-making is a dynamic process, which extends the time and the space. In order to reproduce this kind of naturalistic decision-making process, we devised a joystick-controlled dynamic interactive pursuit task that resembles naturalistic hunting behaviors. To capture real-time changes in neural activity and task conditions, we simultaneously recorded neural activities in the dorsal anterior cingulate (dACC) with 96 channel-floating

microarray and the position of the avatar of the animal and computer-controlled prey. With the rich and complex task conditions we questioned: 1. Is the tuning for task variables in the dACC neurons sustained throughout the trial, or is there a temporal progression? 2. Is there an overlap between the population of neurons coding task variables and whether the tuning for different task variables evolves together? 3. Is the dimensionality of neural representations in such a naturalistic task comparable to other simpler choice tasks (e.g. 2AFC gambling tasks)? Here, we found most neurons in the dACC are tuned to the task variables only transiently in the naturalistic pursuit task. In addition, we found multiplexed neurons that are tuned for different task variables, but the tunings evolved at different times through the trial progression. Despite the high complexity of the task, the dimensionality of neural representations retrieved from dACC activities in the naturalistic pursuit task was only slightly higher than simple economic choice tasks.

Disclosures: J. Tu: None. **S.M. Yoo:** None. **B.Y. Hayden:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.14/EEE3

Topic: H.01. Animal Cognition and Behavior

Title: Foraging behavior and risk preference in freely moving Rhesus macaques

Authors: *B. R. EISENREICH[1], B. Y. HAYDEN[2]
[1]Univ. of Minnesota, Minneapolis, MN; [2]Univ. of Minnesota, Saint Paul, MN

Abstract: Within the natural environment animals face a critical challenge in balancing the costs and benefits of searching for and consuming different food sources, or more generally rewards. Across taxa, risk appears to be a key variable that influences how these judgments are made. One puzzling finding is the tendency of primates to be risk seeking within economic tasks, as a large body of research in other species has found the opposite trend. A possible explanation for this apparent discrepancy is the tendency of using highly controlled tasks that mimic the statistics of the natural environment, while limiting the animal's ability to engage in unrestrained behavior. Here we examined foraging behavior under conditions of risk while allowing primates to move freely about a large cage. Importantly, we demonstrate an approach that allows for the performance of unrestrained behaviors and is compatible with wireless electrophysiology, without having to sacrifice control of the environmental statistics. Our preliminary results are suggestive of risk aversion in primates and highlight the importance of unrestrained behavior on decision-making.

Disclosures: B.R. Eisenreich: None. **B.Y. Hayden:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.15/EEE4

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 Grant DA037229
MINECO Grant BFU2017-85936-P
MINECO Grant FLAGERA-PCIN-2015-162-C02-02

Title: An attentionally-aligned model of value-comparison

Authors: *H. AZAB[1], R. MORENO BOTE[2], B. Y. HAYDEN[3]
[1]Univ. of Rochester, Rochester, NY; [2]Pompeu Fabra Univ., Barcelona, Spain; [3]Univ. of Minnesota, Saint Paul, MN

Abstract: Existing models of value-based choice posit a competition between separate neuronal populations, each dedicated to the stable representation of the value of a particular available option. In maintaining the values of options simultaneously, these models do not account for the role attention plays in making such decisions. Recent studies have shown that single neurons in several prefrontal reward areas as well as the ventral striatum switch between representations of the values of different options depending on which of these is currently the focus of attention. We propose a neuron-level model where a single population of neurons represents the value of the currently attended option, and its value modulates the value representation of subsequent options. In this framework, values are represented relatively rather than in absolute terms, in the context of other options in the environment. This setup allows options to be evaluated in a serial, attention-guided manner. Activity simulated from this model aligns with several findings observed in prefrontal cortex neuronal populations; including mutual inhibition between offer values, as well as representation of sequentially-attended offers in similar formats. We also explore the dynamics of this model when presented with more than two options.

Disclosures: H. Azab: None. **R. Moreno Bote:** None. **B.Y. Hayden:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.16/EEE5

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA039351

Title: The role of the orbitofrontal cortex in expectation and motivation

Authors: *Z. S. GILLIS, E. L. RICH
Dept. of Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Expectations color our perceptions and guide our decision-making. Maladaptive expectations are features of a variety of psychiatric disorders such as major depressive disorder, and can bias behavior towards unfavorable outcomes, making them a prime target for treating mental illness. Currently, the neural mechanisms that give rise to expectations, and how these expectations alter networks involved in perception and decision-making, remain unclear. The OFC is known to encode the value of reward-predictive stimuli, and distinct regions of OFC may serve different functions in updating stimulus values. To better understand the mechanisms through which expectations are formed and updated, we trained two monkeys on a reward expectation task in which pictures served as stimuli predicting rewards with varying levels of sweetness and bitterness. During forced choice trials, only one reward-predictive stimulus was offered. During free choice trials, the subject was presented with two options, which he could choose between. In order to receive an initial reward in either trial type, the subject fixated on a stimulus and simultaneously released a touch sensor bar. The initial reward delivery was followed by a period of 4 seconds, during which the subject could freely tap the bar for small amounts of additional reward. Both subjects formed clear and stable reward preferences, selecting sweeter or less bitter rewards on free-choice trials, and tapping the bar more frequently for more preferred rewards. Therefore, bar tapping provided a time-varying behavioral measure of motivation to earn each reward. To determine whether bar tapping was motivated by expectations or actual rewards received, mismatch trials were included in which the reward delivered was not the expected reward. We found that subjects were initially motivated by expectations, but after a few seconds subjects adjusted their bar tapping, so behavior was better predicted by the actual rewards. Preliminary data from chronic electrophysiological recordings in this task suggest that the OFC is preferentially activated on mismatch trials. Using multi-probe arrays we will record simultaneously from OFC and gustatory cortex to determine how expected values and taste perception dynamically motivate behavior.

Disclosures: Z.S. Gillis: None. **E.L. Rich:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.17/EEE6

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA039351

Title: Representations and dynamics in OFC and ACC in a value based decision making task

Authors: *P. ENEL[1], J. D. WALLIS[2], E. RICH[1]
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Univ. of California Berkeley, Berkeley, CA

Abstract: A long line of research has shown that the orbito-frontal cortex (OFC) and the anterior cingulate cortex (ACC) are heavily involved in value based decision making. However, representations and dynamics of each of these prefrontal areas in this context are still not clear. To better characterize these aspects of neural population activity, we trained two monkeys to perform a decision making task and recorded the activity of OFC and ACC neurons. In this task, visual cues predicting an amount and type of reward were presented to monkeys. Cues represented four different amount of reward, and either a primary reward in the form of juice or a secondary reward represented by the increase of a bar presented on screen at the time of reward. Every 4 trials, monkeys cashed in the secondary reward as an amount of juice equivalent to the size of the bar. In a quarter of the trials, the monkeys were allowed to choose from two reward predicting cues while in the rest of the trials, only one cue was presented. The presentation of the cues and their associated reward were interleaved with a joystick response task introduced to keep monkeys focused. We conducted population analyses of recorded neurons to characterize the representation structures and dynamics associated with different aspects of the task, and contrasted them between OFC and ACC. Preliminary results show a sustained encoding of value and reward type throughout the trial, from cue presentation to reward delivery, including during the unrelated joystick response task.

Disclosures: P. Enel: None. **J.D. Wallis:** None. **E. Rich:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.18/EEE7

Topic: H.01. Animal Cognition and Behavior

Support: CIHR

Title: An analysis of the activity in frontal cortex ensembles during a 3-lever decision making task

Authors: *J. K. SEAMANS[1], E. EMBERLY[2], B. CARACHEO[3]
[1]Psychiatry, UBC, Vancouver, BC, Canada; [2]Simon Fraser Univ., Cancouver, BC, Canada; [3]UBC Brain Res. Ctr., Vancouver, BC, Canada

Abstract: It is often said that the rodent medial prefrontal cortex (mPFC) plays a role in decision making but it is unclear what is involved in this process from a mechanistic point of view. To gain insight into how frontal cortex neurons encode value-based decisions, tetrode recordings were performed while rats tried to determine which one of 3 randomly chosen levers was baited each day. Although the baited lever yielded a pellet every time it was pressed, there was considerable variation across rats with 6/10 exploiting the baited lever within 50-100 trials while the remainder distributed presses across the 3 levers throughout the session. We initially focused on those sessions where rats learned to exploit the baited lever. The decision process was evaluated using a multi-category logistic model where each lever was represented by an energy state as defined by the weighted linear combination of the top 15 principle components of ensemble activity. Based on a subset of trials, the model attempted to maximize the probability that a given energy state was associated with one of the 3 lever choices. The model was then used to predict lever choices based on the ensemble activity during the remaining set of test trials. The time bin where the energy level of a given lever achieved a local minimum was taken as the decision point. We found that the model achieved >95% accuracy in predicting the chosen lever on test trials if it was trained on the 5s window preceding the lever press. This was true regardless of whether the chosen lever was the one that was baited or not. However, when the training window was shifted to the time of the lever press or the time of reward delivery, performance of the model declined significantly. This implied that the ensemble states associated with the decision were different from the ensemble states associated with the lever presses or the outcomes, calling into question the assumption that the neurons 'weighed' each option during the decision process. Ongoing analyses will compare how the decision process varied across sessions with different distributions of lever press choices.

Disclosures: J.K. Seamans: None. **E. Emberly:** None. **B. Caracheo:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.19/EEE8

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Grant MOP-93784
CIHR Grant MOP-84319

Title: How over interpretation of simple behavioral models can lead to unexpected results: In search of the optimal sampling distributions for delay values on the Restaurant Row task

Authors: *N. J. POWELL[1], S. GUPTA[2], A. R. MALHOTRA[2], J. K. SEAMANS[3]
[1]Psychiatry, [2]Univ. of British Columbia, Vancouver, BC, Canada; [3]Psychiatry, UBC, Vancouver, BC, Canada

Abstract: We attempted to utilize an optimal sampling distribution on the restaurant row task (Steiner and Redish 2014) to sample animal's decision behavior as efficiently as possible, but because the sampling distribution lead to changes in the overall economic structure of the task and a more difficult state recognition process, the "optimal" distribution ended up providing less accurate measurements of the animal's underlying preferences. In the Restaurant Row task (Steiner and Redish 2014) animals make sequential wait/skip decisions at 4 feeder locations offering different flavors of food with a randomly chosen delay on each visit. The probability of waiting out a particular delay length vs skipping it is used to determine animal's preference for each food flavor. Specifically, the animal's preferences on this task are modeled by fitting a logistic function to their probability of waiting for a reward as a function of delay length. The threshold values of these logistic functions represent the relative value of each reward option. The longer animals are willing to wait, the more valuable the reward. Previously delay values were sampled randomly from a uniform distribution, which results in a large number of easy decisions (delays well below or above threshold will be accepted or rejected at nearly 100% rates). In order to maximize the information gained from each feeder visit, it would be optimal to sample most heavily near the threshold of the sigmoid function where the information density of each decision is the highest. We therefore used delays chosen from a normal distribution with an adjusting mean matched to the animal's indifference threshold. We compared this to a uniform delay distribution and to a bimodal delay distribution where delays were primarily either below or above the indifference threshold (which was helpful for training purposes). Although overall flavor preferences seemed to be similar no matter which sampling distribution was used, we found the "optimal" sampling pattern to be the least accurate at revealing underlying flavor preferences because the distinctions between delay values for the "optimal" distribution were the least clear, and the absence of extreme decisions changed the economic framework of the task in unanticipated ways. This example is a useful reminder that although behavior may be summarized by a simplified mathematical model, full behavioral effects are only realized by considering the interactions of multiple different systems working together as a complex whole.

Disclosures: N.J. Powell: None. **S. Gupta:** None. **A.R. Malhotra:** None. **J.K. Seamans:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.20/EEE9

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant R01MH112746
Sir Henry Wellcome Fellowship from the Wellcome Trust (098830/Z/12/Z)
Wellcome Trust New Investigator Award (096689/Z/11/Z)
Middlesex Hospital Medical School General Charitable Trust
NSERC Postgraduate Scholarships-Doctoral Program

Title: A circuit mechanism for pro-variance bias in decision-making: Behavior, computational modeling, and pharmacology

Authors: *N. H. LAM[1], S. E. CAVANAGH[3], L. T. HUNT[4], S. KENNERLEY[3], J. D. MURRAY[2]
[1]Physics, [2]Dept. of Psychiatry, Yale Univ., New Haven, CT; [3]Sobell Dept. of Motor Neurosci., Univ. Col. London, London, United Kingdom; [4]Wellcome Ctr. for Integrative Neuroimaging, Dept. of Psychiatry, Univ. of Oxford, Oxford, United Kingdom

Abstract: In perceptual or value-based decision-making tasks, noisy stimuli can lead subjects to accumulate evidence across time as a decision strategy. In such paradigms, choice behavior can exhibit pronounced biases departing from optimal integration. In this study, we combined computational modeling of neural circuits with psychophysical choice behavior, and its alteration by pharmacology, to investigate the mechanisms of evidence accumulation in decision-making. Two monkeys (Macaca mulatta) were trained to perform a two-alternative forced-choice task. In each trial, the animal was required to discriminate the mean heights of two vertical bars whose heights varied every 250ms, with 4 or 8 samples. Critically, the sample variance for one option's stream of evidence was twice as large as the other. We found that the animals exhibited a bias in their choices toward the option with larger variance, i.e. a pro-variance bias (PVB) effect. Decision-making performance was also studied under pharmacological manipulation by subanesthetic administration of the NMDA receptor antagonist ketamine.
To investigate a potential circuit mechanism underlying the PVB, we analyzed a biophysically-based computational model of a spiking cortical circuit which was previously applied to temporal integration of evidence in perceptual decision-making (Wang, 2002). The model also exhibited a PVB, with similar magnitude to the monkeys, demonstrating a potential circuit mechanism of the PVB which is intrinsic in recurrent decision-making dynamics. Nonlinear dynamical systems analysis of a mean-field approximation provides a mechanistic explanation of the PVB in the model: strong stimuli have an asymmetrically larger effect than weak stimuli.
To relate the circuit model to the empirical ketamine behavior, we characterized the effects of NMDA receptor antagonism at two key synaptic sites: inhibitory interneurons, elevating excitation-inhibition (E/I) ratio; versus excitatory pyramidal neurons, lowering E/I ratio. We found these distinct E/I perturbations induced dissociable effects in the psychophysical kernel and PVB. In the empirical data, ketamine administration degraded performance through overall reduced sensitivity to the stimulus, but increased the weighting of stimulus variance on choice relative to the mean stimulus value. In the circuit model, we found that this pattern of behavior is consistent with lowered E/I ratio weakening accumulation of evidence. These results suggest a neural circuit mechanism for PVB in decision-making, with implications for cognitive deficits in neuropsychiatric disorders associated with cortical E/I dysfunction.

Disclosures: N.H. Lam: None. **S.E. Cavanagh:** None. **L.T. Hunt:** None. **S. Kennerley:** None. **J.D. Murray:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.21/EEE10

Topic: H.01. Animal Cognition and Behavior

Support: Sir Henry Wellcome Fellowship from the Wellcome Trust (098830/Z/12/Z)
Wellcome Trust New Investigator Award (096689/Z/11/Z)
Middlesex Hospital Medical School General Charitable Trust

Title: Behavioural and neural evidence for irrational biases during evidence accumulation decisions

Authors: *S. KENNERLEY[1], L. T. HUNT[2], S. E. CAVANAGH[1]
[1]Univ. Col. London, London, United Kingdom; [2]Univ. of Oxford, Oxford, United Kingdom

Abstract: The gradual accumulation of noisy evidence is a fundamental component of decision-making. Recent work has used tasks where subjects must count the number of evidence pulses (e.g. auditory clicks) corresponding to two choice options during a stimulus period and choose which had the most cumulative evidence supporting it when cued to respond. Humans and rats use an optimal strategy to solve these decisions, assigning equivalent weighting to evidence received throughout the stimulus period (Brunton et al. 2013). However, when combining multiple pieces of information in real-world decisions, the number of different pieces of evidence favouring each option cannot merely be counted. Instead, evidence of different sizes and valences must be accumulated to form an overall integrated value associated with each choice option. Using a more complicated task where subjects must average across multiple pieces of evidence with distinct magnitudes, systematic irrationalities in human decision-making have been characterised (Tsetsos et al. 2016). We employed a similar task design in macaque monkeys to allow us to study the neural basis of these irrationalities. Two monkeys (Macaca mulatta) were trained on a two-alternative value-based evidence integration task. A series of bars, each with different heights, were presented on the left and right-side of a computer monitor (200ms presentation; 50ms interval).The number of sample presentations was either four or eight in different trial blocks. Following a post-stimulus delay (500±250ms), subjects were cued to choose one of the two options. Before the bars were presented, a cue instructed the subjects whether choosing the option with either the highest (High Context) or lowest (Low Context) average bar-height would be rewarded. Subjects displayed a high level of performance on this challenging task; where both the number of samples to integrate and the contingency (High v Low Context) was changing across blocks of trials. Regression analysis showed subjects were

using the average bar height in the stream to guide their choices; rather than counting the number of individual frames favouring either option. However, they also displayed two key irrational behavioural biases. Firstly, subjects overweighted stimuli early in the trial - resulting in a *primacy bias*. Secondly, subjects preferred to choose options with a greater variance in evidence strength across the sample stream: *pro-variance bias*. We will investigate the neural basis of these biases, as well as contrasting the roles of different brain areas in evidence accumulation, by simultaneously recording single-neurons across Prefrontal and Parietal Cortex.

Disclosures: S. Kennerley: None. **L.T. Hunt:** None. **S.E. Cavanagh:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.22/EEE11

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Strategic Award Grant WT101092MA
Medical Research Council Grant MR/K005480/1

Title: An investigation of predictive coding and behavioural flexibility in the primate prefrontal cortex using multi-area, multi-electrode electrophysiological methods

Authors: *E. BOSCHIN, J. M. GALEAZZI GONZALEZ, M. O'NEILL, Z. WU, M. J. BUCKLEY
Univ. of Oxford, Oxford, United Kingdom

Abstract: Individual neurons are capable of encoding expectations about events, for example the probability of receiving a reward following an action; furthermore, they encode prediction errors when these expectations are not met, for example when a reward is not received after an action that was previously rewarded. These prediction errors are then used to compute a new, updated prediction, about the likelihood of that event. The continuous loop of predictions, prediction errors and updates, is a type of computation crucial for learning and flexible, adaptable behaviour. Single-cell neurophysiological recordings in monkeys have demonstrated that several prefrontal areas are involved in coding predictions and prediction error information. However, the study of each area in isolation has so far not allowed for elucidating how interactions between brain regions give rise to predictive mechanisms that support learning and flexible behaviour.
Here, we introduce the first study that seeks to address these questions by applying multi-electrode techniques to different frontal regions in the macaque monkey. We present exploratory results from two 64-electrode micro-arrays (‘Utah arrays’) implanted in the anterior cingulate gyrus (ACC) and dorsolateral prefrontal cortex (dlPFC), which allowed us to record both single-

and multi-unit activity, as well as local field potentials, simultaneously from both areas, while the monkey is engaged in a novel two-step navigation task within a virtual dynamic maze involving probabilistic decision-making and flexible updating of behavioural plans.
For each array, we obtained a substantial yield of about 70-80 clusters comprising single-unit and multi-unit activity. Within these clusters, we identified units that respond to task-relevant aspects of the task - such as, for example, reward and reward expectation (in both ACC and dlPFC) and state transitions (in dlPFC) - and oscillatory activity in the beta and gamma bands that appear consistent with current predictive coding theories of how predictions versus prediction errors might be transmitted across networks of neuronal populations. We discuss these findings in the context of our current understanding of predictive coding models, as well as with regards to future applications of the task to further investigate these mechanisms in other brain regions and in combination with more advanced analytical tools to address network-level dynamics.

Disclosures: E. Boschin: None. **J.M. Galeazzi Gonzalez:** None. **M. O'Neill:** None. **Z. Wu:** None. **M.J. Buckley:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.23/EEE12

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Strategic Award Grant Ref: WT101092MA
MRC Project Grant Ref: MR/K005480/1

Title: Multi-neuronal, multi-area, neurophysiological interactions underlying dynamic stimulus- and action-value coding in the macaque prefrontal cortex during learning and decision making

Authors: *M. O'NEILL, E. A. BOSCHIN, J. M. GALEAZZI GONZALEZ, Z. WU, ESQ, M. J. BUCKLEY
Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Individual neurons are capable of encoding integrated value signals that are essential to inform learning and guide decisions. For example, the expected value of receiving a reward following a stimulus or an action encoded as the product of the probability and magnitude of the expected outcomes. These values signals can be used to compute a behavioural choice, and combined coding of stimulus and action values is a type of computation crucial for learning and flexible, adaptive behaviour.
Single-cell neurophysiological recording studies have demonstrated that several prefrontal areas are involved in coding stimulus and action values. However, the study of each area in isolation

does not address how interactions between brain regions give rise to integrated value signals that support learning.
We present the first study that applies multi-electrode techniques simultaneously to four different regions in prefrontal cortex to show how interactions within and between these regions facilitates information processing and transfer about different types of value signals across the network to drive learning and decisions.
We developed a Stimulus To Action Response Task (START) that facilitates dissociation of stimulus- and action-values while macaques learn to associate stimuli and actions with probabilistic rewards. Moreover, START reveals dissociable effects on behaviour: preferences for actions based on stimuli are learnt rapidly within sessions, whereas differences in reaction times develop over days (between sessions) as habit behavior begins to form. This behavioural dissociation provides us with a means to compare goal-directed and habit-based neuronal correlates of behavior.
Four multi-electrode micro-arrays were implanted in ventrolateral prefrontal cortex (x96), dorsolateral prefrontal cortex (x32), orbitofrontal cortex (x96), and frontopolar cortex (x32) of the macaque, allowing us to record both single- and multi-unit activity, as well as local field potentials, simultaneously from all four areas, while the monkey performs START. We obtained a substantial yield of 130-140 clusters from each of the 96 electrodes in OFC and vlPFC, and 30-40 clusters from each of the 32 electrodes in FPC and dlPFC. Within these clusters, we identified units that respond to event-related aspects of the task such as visual cues (predicting rewards) and juice rewards, and oscillatory activity in the beta-gamma bands evoked by cues and rewards in OFC, and rewards in vlPFC, dlPFC and FPC. These observations are consistent with the suggestion that OFC is predominantly involved in learning cue-reward associations relevant for goal-based decision-making processes.

Disclosures: M. O'Neill: None. **E.A. Boschin:** None. **J.M. Galeazzi Gonzalez:** None. **Z. Wu:** None. **M.J. Buckley:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.24/EEE13

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Strategic Award Grant Ref: WT101092MA
MRC Project Grant Ref: MR/K005480/1

Title: Exploring the underlying computations and functional interactions of macaque prefrontal areas in rule-based decision making: Recording simultaneously from multiple chronically implanted multi-electrode arrays

Authors: *J. M. GALEAZZI, *J. M. GALEAZZI GONZALEZ, E. A. BOSCHIN, M. O'NEILL, Z. WU, M. J. BUCKLEY
Univ. of Oxford, Oxford, United Kingdom

Abstract: Previous studies have identified several prefrontal areas that contribute to separable cognitive processes in rule-guided behavior. Using a Wisconsin Card Sorting Test (WCST) analog, it has been suggested that the dorsolateral prefrontal cortex (dlPFC) plays an important role in maintaining the representation of an abstract rule in working memory while the ventrolateral prefrontal cortex (vlPFC) supports rule implementation. The orbitofrontal frontal cortex (OFC) plays a prominent role in rapid updating representations of rule value based on reward, while the anterior cingulate cortex (ACC) plays a key role in executive task control, integrating information for correct and incorrect trials. Moreover, recent studies exploring the role of the frontopolar cortex (FPC) suggest a key role in representing the relative value of unchosen alternative rules or stimuli. As neuronal activity from these different areas was not previously recorded simultaneously we do not yet understand the underlying computations and functional interactions operating within and between these regions. We present here the first study that applies multi-area multi-electrode recording techniques to five different frontal regions implicated in rule-guided behaviour. Multi-electrode micro-arrays ('Utah arrays') were chronically implanted in dlPFC, vlPFC, OFC, ACC and FPC of the macaque, allowing us to simultaneously record single and multiunit activity and local field potential (LFP) from all five regions while the monkey performs a WCST analog. Here we present preliminary results showing the neural activities underlying the representation of abstract rules. We obtained a typical daily yield of 90-110 separable clusters from all arrays combined, with single and multiunit activity responsive to different task-relevant components. For example, we found pre-reward and post-reward unit responses in dlPFC and vlPFC, in some cases signaling expected reward delivery and maintaining this firing activity. In OFC, we predominantly observed units with more delayed post-reward response. These responses are consistent with a role of dlPFC and vlPFC in maintaining abstract rule representations; wheras OFC responses update after the reward has been delivered to determine rule value. We found similar patterns in FPC, including units with pre-reward firing followed by an immediate decay. We also found a modulation of LFPs within beta and gamma bands in FPC, whereas power increases in delta and theta were observed in dlPFC, vlPFC and OFC. We discuss these findings and provide a theoretical framework of how these regions interact.

Disclosures: J.M. Galeazzi Gonzalez: None. **E.A. Boschin:** None. **M. O'Neill:** None. **Z. Wu:** None. **M.J. Buckley:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.25/EEE14

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Strategic Award: WT101092MA
MRC Project Grant: MR/K005480/1

Title: The effects of frontopolar cortex lesions on resting state functional connectivity networks in non-human primates

Authors: *M. J. BUCKLEY, M. AINSWORTH, A. BELL, Z. WU
Oxford Univ., Oxford, United Kingdom

Abstract: Recent lesion studies demonstrate that macaque frontopolar cortex (FPC) plays essential roles in mediating exploration and rapid learning about the relative value of alternatives of a broad kind (Boschin et al., 2015; Mansouri et al., 2015; 2017). However, little is known about the influence of FPC upon whole brain networks. Resting state functional connectivity (rsfc) analyses examine the correlations in spontaneous brain activities in the absence of external stimuli or task demands and so offer a tool for understanding functional organization across whole brain networks. In our study, we performed rsfc scans on thirteen monkeys (control group) once, and seven other monkeys (FPC lesion group) post-operatively (eight weeks after lesions). By applying a fine-scale atlas to parcellate macaque brain regions (Van Essen et al., 2011), we acquired rsfc data from 260 regions in both lesion and control groups. We first applied a brain-wide search for the difference between the two groups using a non-parametric permutation test, which revealed that there were 59 regions wherein significant changes in rsfc with other areas were identified. Most of the functional connections among the 59 regions were enhanced in the lesion group compared with the control group. To aid visualization, we applied K-means clustering to further divide the 59 regions into 8 clusters, roughly corresponding to frontal, somatosensory, parietal, cingulate and temporal regions. By applying multidimensional scaling analysis, most of the clusters fall closer together in scaled space in the lesion group compared with the control group. Specifically, connectivities between frontal and other regions (e.g. somatosensory, temporal, parietal) were typically enhanced, while decreased connections were typically observed between cingulate, somatosensory and temporal regions. We interpret these results in the context of FPC-mediated influence on brain networks extending both within and beyond prefrontal cortex.

Disclosures: M.J. Buckley: None. **M. Ainsworth:** None. **A. Bell:** None. **Z. Wu:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.26/EEE15

Topic: H.01. Animal Cognition and Behavior

Support: Wharton Neuroscience Initiative

Title: ACC LFP-aided decoding of EEG signals during sequential foraging decisions

Authors: *A. RAMAKRISHNAN, D. BERKAY, M. L. PLATT
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Food, water and other essential resources are often distributed in spatially localized patches in the environment and foraging animals must choose whether to continue staying in a depleting patch or to leave for a richer one. The marginal value theorem (MVT) provides a normative approach to maximize energy intake by determining the optimal time to depart a patch based on the overall richness of the environment. Although animals, including humans, obey the MVT on average, they display systematic individual differences in foraging behavior. Stress, anxiety or subclinical psychiatric conditions like depression may underlie these behavioural biases. Understanding the neural basis of foraging decisions may help to determine biomarkers to identify these biases and develop possible interventions to mitigate them. Previously, in our lab, we measured neuronal spiking activity in primate dorsal anterior cingulate (dACC) - a brain region involved in monitoring reward and exercising cognitive control. We found that dACC neurons encoded a decision variable that signalled the relative value of leaving a depleting resource for a new one, and Kolling et al 2012 identified a similar signal in foraging humans using fMRI. Here we build on and extend these findings by examining ACC local field potentials (LFPs) - that reflect the input signals to the ACC and contribute to the scalp EEGs - for information guiding foraging decisions. To do this, we obtained LFPs from 2 NHPs using linear multichannel arrays and identified the relevant temporal and spectral components of the LFP-based decision signal. We also obtained EEG from 45 human participants using a modified Emotiv wireless EEG device performing the same foraging task and assessed the feasibility of identifying the relevant LFP components in the EEG signal. Preliminary results suggest that LFPs indicate when and whether NHPs will choose to abandon a patch. Strong modulations in the theta, beta and gamma bands were observed around the time of leave decisions. A supervised machine learning algorithm trained on LFPs could predict decision time significantly better than chance. Next we will identify and extract the relevant signal components from the above-mentioned algorithm to inform EEG data analysis to predict biases in foraging decisions.

Disclosures: A. Ramakrishnan: None. **D. Berkay:** None. **M.L. Platt:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.27/EEE16

Topic: H.01. Animal Cognition and Behavior

Support: Wharton Neuroscience Initiative

Title: Using EEG and pupillometry in a foraging task to establish biomarkers for anxiety

Authors: *D. BERKAY, A. RAMAKRISHNAN, J. A. STYLLI, M. L. PLATT
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Reward maximization while foraging is a crucial problem all animals, including humans, need to solve. Although both human and non-human animals adopt optimal foraging strategies on average, individuals vary considerably in their foraging behavior. Variation in the fundamental computations underlying foraging may provide a powerful opportunity to identify biomarkers of neural circuit dysfunctions associated with mental disorders, thereby obviating the need to obtain self-report and potentially providing deeper insights into the neural mechanisms that cause neuropsychiatric disorders. A neural circuit connecting posterior and anterior cingulate cortices with norepinephrinergic neurons in the locus coeruleus has been implicated in variation in foraging behavior. This circuitry is also associated with anxiety disorders, suggesting a possible biological connection between the two. To test this idea, we measured the behavior of human participants performing a patchy foraging task where they made stay/leave decisions in environments varying in richness, while we monitored pupil size, which indexes norepinephrine tone, and EEG-based frontal theta band signals associated with anxiety. Anxiety was assessed by self-report using the State-Trait Anxiety Inventory. We found that a supervised machine learning algorithm could predict anxiety scores using patch leaving time, pupil diameter, and EEG theta band power. To test the functional links between these potential biomarkers and anxiety levels, we conducted a second study in which we exposed participants to physical and social stress and then measured changes in behavior. Preliminary results reveal that increasing anxiety through stress induction provokes earlier patch leaving times. Together, our results show that both momentary and long-term anxiety can be decoded from EEG and pupil dynamics during foraging, reflecting computations that are fundamental to the behavior, and ultimately, biological success of all animals. These findings may provide new approaches for early detection of neuropsychiatric disorder onset, monitoring response to treatment, and relapse prevention, particularly in individuals, such as children, for whom self-report is less reliable.

Disclosures: D. Berkay: None. **A. Ramakrishnan:** None. **J.A. Stylli:** None. **M.L. Platt:** None.

Poster

688. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 688.28/EEE17

Topic: H.01. Animal Cognition and Behavior

Support: NSERC DG

AIHS

Title: Decoding spatial position reveals prospection and working memory in rodent rat cingulate cortex

Authors: *A. J. GRUBER[1], A. MASHHOORI[2], D. R. EUSTON[3]
[1]Dept. of Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Univ. of Lethbridge, Lthbridge, AB, Canada; [3]Univ. Lethbridge, Lethbridge, AB, Canada

Abstract: The anterior cingulate cortex (ACC) encodes information supporting mnemonic and cognitive processes. Moreover, individual ACC cells in rodents have very broad representation of space. We show here that ensemble ACC activity in a behaving rat can be decoded via machine learning to accurately predict an animal's position on a track with high spatiotemporal resolution. A deep neural network was over 30% more accurate than a Bayesian decoder. ACC neurons encoded the current state of the animal and task, except for brief excursions that sometimes occurred at target feeders. During excursions, the decoded position became more similar to a remote target feeder than the rat's physical position. Excursions recruited activation of neurons encoding choice and reward, and the likelihood of excursions at a feeder was inversely correlated with feeder preference. These data suggest that the excursion phenomenon was related to evaluating real or fictive choice outcomes, particularly after disfavoured reinforcements, similar to proposals derived from experiments in primates. We propose that the multiplexing of position with choice-related information forms a mental model isomorphic with the task space (e.g. a cognitive map), which can be mentally navigated via excursions to recall multimodal information about the utility of remote locations. We suggest this dynamical phenomenon may be a form of prospection. We further found that controlling for position-related variance of neural firing revealed evidence of a memory trace that could disambiguate the sequential context of a common running trajectory in a multi-trajectory sequence task. We suggest that this is a working memory. In sum, we propose that encoding of spatial aspects of a task in ACC serves as a framework for the encoding of memories over short and long time scales.

Disclosures: A.J. Gruber: None. **A. Mashhoori:** None. **D.R. Euston:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.01/EEE18

Topic: H.01. Animal Cognition and Behavior

Support: The Kavli Foundation
Norwegian Research Council

Title: Early network dynamics underlying the maturation of the medial entorhinal cortex

Authors: *F. DONATO, S. G. COGNO, H. A. OBENHAUS, R. I. JACOBSEN, M.-B. MOSER, E. I. MOSER
Kavli Inst. For Systems Neurosci., Trondheim, Norway

Abstract: The medial entorhinal cortex (MEC) contains the basic elements of the brain's representation of space. The most abundant cell type contributing to this representation is the grid cell, which is active at multiple spatial locations (fields) that are arranged in a hexagonal pattern tiling the entire available environment. Since no external stimuli occur with a grid-like pattern, this periodic firing is likely generated by intrinsic network computations supported by local microcircuit connectivity. Grid cells exhibiting correlated firing in one context (i.e., grids of the same module and with the same fields location) are still correlated when the animal explores a different enclosure, or when activity is driven by self-organized dynamics during sleep. This suggests that synaptic connectivity in the network is hard-wired into a topology that supports the regular firing of grid cells. However, the regular firing of grid cells emerges at the end of a protracted period during postnatal life that coincides with the structural and functional maturation of the network. The mechanisms underlying the developmental refinement of the grid map are still unknown: cells with correlated firing could be pre-configured to connect preferentially based on their developmental origin; alternatively, synchronous firing might emerge during maturation to shape functional connectivity. Here, we want to investigate how correlated activity among ensembles of neurons evolves in the developing MEC network (P14-P35). To this end, we induce the expression of a genetically encoded calcium indicator through an ultrasound-guided viral injection on postnatal day 1, and image the activity of large populations of neurons in layer two of the MEC while mice perform a spontaneous locomotor task under a 2-photon microscope. Our results indicate the presence of subsets of neurons that repeatedly fire together from P14 on. The number of subsets, the number of neurons that each subset contains and how robust those subsets are changes with maturation. This suggests that early network dynamics shape the connectivity, and thus the correlation structure, of the entorhinal network. Nevertheless, preconfigured ensembles might account for the subsets of correlated neurons observed early during development.

Disclosures: F. Donato: None. **S.G. Cogno:** None. **H.A. Obenhaus:** None. **R.I. Jacobsen:** None. **M. Moser:** None. **E.I. Moser:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.02/EEE19

Topic: H.01. Animal Cognition and Behavior

Support: Kavli Foundation
Norwegian Research Council Centre of Excellence Grant
NIH Grant R01 MH094146

Title: Episodic time coding in lateral entorhinal cortex

Authors: *A. TSAO[1], J. SUGAR[1], L. LU[1], C. WANG[2], J. J. KNIERIM[2], M.-B. MOSER[1], E. I. MOSER[1]
[1]Kavli Inst. for Systems Neurosci., Trondheim, Norway; [2]Zanvyl Krieger Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: The encoding of time and the binding of time to events are critical components for episodic memory, but how these processes are carried out within the hippocampal-entorhinal circuit is still unclear. Here, we investigated temporal coding in lateral entorhinal cortex (LEC). We focused on LEC because (i) this area is a major source of cortical input to the hippocampus, (ii) previous work has shown that responses in LEC to physical stimuli could be unstable across time, and (iii) a clear underlying function has not yet been defined for LEC. We recorded neural activity for more than an hour while rats ran in a box whose walls alternated between black and white over 12 trials (461 cells from 3 male rats). An extended number of trials was used to increase the likelihood that animals defined multiple temporal contexts across the experiment, and to allow the effects of wall color to be separated from the effects of any temporal coding. We previously found that temporal information was robustly encoded within the overall population state in LEC during free behavior, and widely distributed across the entire LEC population through cells exhibiting classical linear selectivity for time as well as cells exhibiting mixed selectivity for time and other external features (Tsao et al., SfN 2017). We have now examined LEC activity at both the single-cell and population level in more detail. At the single-cell level, for cells exhibiting selectivity for time in the form of ramping activity, we measured their time constants, and found that they spanned a wide range, suggesting that this subpopulation of cells is capable of carrying temporal information across a wide range of timescales. At the population level, we characterized the evolution of population activity in LEC using various distance measures on population activity states and found that population activity changed in a manner reflecting the animal's experience, as opposed to trivial noise. We previously also reported on changes in LEC activity at the single-cell level when animals' experiences were constrained by structured behavioral tasks to be similar across repeated trials. We have now looked at population-level encoding of time during these tasks, and find that the encoding of temporal flow across trials was reduced while the encoding of relative passage of time within single trials was improved (334 cells from 5 male rats), suggesting that temporal information arises inherently from the representation of experience being generated in LEC. Overall, the temporal information we observe in LEC may be integrated with spatial inputs from MEC in the hippocampus, allowing the hippocampus to store a unified representation of what/where/when.

Disclosures: A. Tsao: None. **J. Sugar:** None. **L. Lu:** None. **C. Wang:** None. **J.J. Knierim:** None. **M. Moser:** None. **E.I. Moser:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.03/EEE20

Topic: H.01. Animal Cognition and Behavior

Support: Kavli Foundatrion
EuropeN Research Council
Research Council of Norway

Title: Object-vector coding in medial entorhinal cortex: Object shape and object dimensions

Authors: E. R. SKYTØEN[1], Ø. A. HØYDAL[2], S. O. ANDERSSON[1], *E. I. MOSER[3,1], M.-B. MOSER[1]
[2]Kavli Inst. for Systems Neurosci. and Ctr. for Neural Computation, Norw, [1]NTNU, Trondheim, Norway; [3]Kavli Inst. Systems Neurosci, Trondheim, Norway

Abstract: Mammals use distances and directions from local objects to guide navigation, but how such vector-based navigation strategies are implemented in neural representations of space has not been resolved. Recently, we reported that a class of cells in the medial entorhinal cortex (MEC) encodes allocentric vectors to discrete objects in the environment (Høydal et al., SfN 2017). Recordings from more than 500 MEC cells in more than 8 adult male C57B6 mice show that such 'object-vector cells' (more than 100) fire whenever the animal is at a certain direction and distance relative to an object, independently of the direction of movement through the location and independently of whether objects are novel or familiar. When the object is displaced, the firing fields of object-vector cells move accordingly, so that tuning to object distance and direction remains constant. Object-vector encoding occurs irrespective of object identity, but exactly how object shapes and dimensions influence the firing properties of the cells has not been determined. To address this question, we recorded object-vector cells in the MEC of freely moving male mice while systematically varying the size of objects in the animal's proximal environment. Our data show that object-vector cells respond strongly to objects that vary more than an order of magnitude in diameter (for cylinders), length (for prisms with a rectangular base), or height (for prisms with a square base). We found no strong tendency for object-vector cells to encode specifically vectors from objects of any particular shape or dimension, except that tall objects elicited more firing than flat objects of similar width. A small subset of object-vector cells also responded to peripheral walls of the recording box (border cells) but for such cells there was often no correlation between distance and direction from object and wall, respectively, suggesting that object-vector cells respond to a wider class of objects, with other properties, than border cells and boundary-vector cells. Collectively, our observations show that object locations are integrated into metric representations of self-location, with

specific subsets of MEC neurons encoding vector relationships to individual objects of a wide range of shapes and dimensions.

Disclosures: E.R. Skytøen: None. **Ø.A. Høydal:** None. **S.O. Andersson:** None. **E.I. Moser:** None. **M. Moser:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.04/EEE21

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH097130-05
Kavli Foundation, the Centre of Excellence scheme of the Research Council of Norway – Centre for Biology of Memory and Centre for Neural Computation, The Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits
National Infrastructure scheme of the Research Council of Norway – NORBRAIN

Title: The relationship between the relative firing rates of individual grid fields and hippocampal remapping

Authors: *C. LYKKEN[1], B. R. KANTER[1], J. DICKINSON[2], K. ASUMBISA[1], C. G. KENTROS[1]
[1]Kavli Inst. for Systems Neurosci., NTNU, Trondheim, Norway; [2]Inst. of Neurosci., Univ. of Oregon, Eugene, OR

Abstract: Place cells in the hippocampus fire action potentials in specific locations in the environment. They are stable across repeated exposures to the same environment, but they remap in distinct environments, exhibiting unpredictable changes in their firing rate and/or location. Under the same conditions that elicit remapping, the hexagonal pattern of grid cells in medial entorhinal cortex (MEC) layer II (a main input to the hippocampus) shifts and/or rotates (Fyhn et al., 2007). However, all evidence thus far indicates that grid cells shift coherently, which is therefore incapable of producing the orthogonal spatial representation observed during hippocampal remapping. We recently uncovered an additional mechanism whereby changes in the firing rates of individual grid fields drive remapping of place cells, even when grid field locations remain stable (Kanter et al., 2017). We did this by manipulating the activity of a subset of MEC layer II neurons using transgenic expression of an hM3Dq DREADD (Designer Receptor Exclusively Activated by Designer Drugs). Injection of the designer ligand clozapine-N-oxide (CNO) depolarizes MEC neurons and causes remapping of CA1 place cells in a familiar environment. Here, we further explore the relationship between grid field firing rate changes and place cell remapping. First, we show that changing the firing rates of individual grid fields is

sufficient to cause remapping in a winner-take-all model of grid-to-place cell formation (de Almeida et al., 2012). Furthermore, in both experimental and simulated data, we can successfully predict where a place cell will remap to based on its activity pattern before CNO administration. We then demonstrate that the dynamics of the CNO-induced remapping tightly correlate with the CNO-induced changes in grid field firing rates. More specifically, we observed that the changes in grid field firing rates and the remapping in CA1 both exhibited high short-term stability. Over several hours, however, there were subtle changes in the rankings of individual grid fields that were concomitant with a partial reduction in the stability of the CNO-induced remapping. Critically, when the rankings of individual grid fields reset following an extended break in the recording, place cells also resumed their baseline firing patterns. Finally, we demonstrate that repeating our manipulation (by injecting CNO again the following day) elicited similar changes in grid field firing rates and place field locations, which is also recapitulated by our model. Taken together, we provide strong evidence that the firing rates of individual grid fields play an important role in determining place field location.

Disclosures: C. Lykken: None. **B.R. Kanter:** None. **J. Dickinson:** None. **K. Asumbisa:** None. **C.G. Kentros:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.05/EEE22

Topic: H.01. Animal Cognition and Behavior

Support: European Research Council:Grant Agreement N°338865
European Research Council: Grant Agreement N°268598
Research Council of Norway: grant no. 226003
Centre of Excellence scheme and the National Infrastructure Scheme of the Research Council of Norway: grant number 223262
Louis Jeantet Prize
The Korber Prize
The Kavli Foundation

Title: Functional characterization of neurons in layer V of the medial entorhinal cortex

Authors: *D. C. ROWLAND[1], H. A. OBENHAUS[1], R. R. NAIR[1], C. G. KENTROS[2], E. I. MOSER[3], M.-B. MOSER[3]
[2]Kavli Inst. for Systems Neurosci., [1]NTNU, Trondheim, Norway; [3]Kavli Inst. Systems Neurosci, Trondheim, Norway

Abstract: Layer V of the medial entorhinal cortex (MEC) consists of two sublayers: a superficial layer Va and a deep layer Vb (Sürmeli et al., 2015). The principal cells in these two sublayers differ dramatically in their morphology, gene expression and connectivity. Most notably, Layer Va is the nearly exclusive output from the MEC to areas outside the hippocampal and parahippocampal region, including the prefrontal and retrosplenial (RSC) cortices. In contrast, layer Vb cells appear to project mainly within the entorhinal cortex. Although layer Vb cells project mostly locally, they receive input from both hippocampal and non-hippocampal sources, positioning them as key integrators in the circuit. Therefore, knowing the functional properties of cells in these two sublayers is critically important for understanding local computations within the MEC and the contribution of the MEC to the global network. To address the functional properties of layer Va cells, we used AAV-retro viruses (Tervo et al., 2016) carrying ChR2/H134R into the RSC of wild-type mice and targeted optrodes to layer Va of the MEC (Rowland et al., SfN, 2017). The retrograde spread of the modified virus from the RSC to the MEC labelled layer Va cells nearly exclusively and allowed us to identify the cells in vivo using an optogenetic tagging approach. The identified Va cells displayed high levels of mixed selectivity. The tagged Va cells were most often informative of some combination of position, direction and running speed, but were rarely canonical grid cells or head direction cells. Thus, the output from the MEC appears to be a multiplexed representation of position, direction and speed. To target layer Vb cells, we turned to a new transgenic mouse line that expresses tTA nearly exclusively in layer Vb of the entorhinal cortex (Blankvoort et al., 2018) and injected these mice with a tTA-dependent virus carrying the channelrhodopsin-2 variant oChief for optogenetic tagging. Functional characterization of this line is in progress.

Disclosures: D.C. Rowland: None. **H.A. Obenhaus:** None. **R.R. Nair:** None. **C.G. Kentros:** None. **E.I. Moser:** None. **M. Moser:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.06/EEE23

Topic: H.01. Animal Cognition and Behavior

Support: European Research Council: Grant Agreement N°338865
European Research Council: Grant Agreement N°268598
Research Council of Norway: grant no. 226003
Centre of Excellence scheme and the National Infrastructure Scheme of the Research Council of Norway: grant number 223262
Louis Jeantet Prize
The Korber Prize
The Kavli Foundation

Title: Miniaturized two-photon microscopy enables the study of functional network topography in the medial entorhinal cortex

Authors: *H. A. OBENHAUS[1], T. ROSE[2], W. ZONG[3], A. TSAO[4], F. DONATO[1], Ø. A. HØYDAL[1], P. M. GOLTSTEIN[2], M.-B. MOSER[1], L. CHEN[3], H. CHENG[3], E. I. MOSER[1], T. BONHOEFFER[2]
[1]Moser Group, Kavli Inst. For Systems Neurosci., Trondheim, Norway; [2]Synapses – Circuits – Plasticity, Max Planck Inst. of Neurobio., Planegg-Martinsried, Germany; [3]State Key Lab. of Membrane Biol., Inst. of Mol. Medicine, Peking-Tsinghua Ctr. for Life Sciences, Beijing Key Lab. of Cardiometabolic Mol. Medicine, Peking Univ., Beijing, China; [4]Dept. of Biol. Sciences, Dept. of Applied Physics, James H. Clark Ctr. for Biomed. Engin. and Sci., Stanford, CA

Abstract: The medial entorhinal cortex (MEC) is thought to create a map of local space using a set of functionally specific and largely distinct cell types: grid cells, head direction cells, border cells, speed cells, and object-vector cells. If and how the functional characteristics of those various cell types are reflected in the anatomical organization of the MEC network is still under debate, however. A non-random anatomical organization would be consistent with the patchy organization of entorhinal layer 2 (Burgalossi et al., 2011) as well as reports of anatomical clustering among grid cells (Heys et al., 2014). Yet a clear understanding of the broader organization of the multi-cell-type network, at both micro and macroscales, has been held back by the absence of suitable neurophysiological methods. While single-unit electrophysiological recordings in freely moving animals enable the precise characterization of cellular firing properties, anatomical relationships can only be indirectly inferred. In vivo two-photon calcium imaging allows for the quantification of firing behaviors of large numbers of simultaneously recorded neurons as well as their precise anatomical organization. However, current two-photon microscopy systems require the animal to be head-fixed and spatial tuning is then inferred from navigation in virtual environments, which have been shown by a number of groups to be problematic for the analysis of spatially selective neurons. Here we show results from imaging large areas of MEC in more than five C57Bl6 mice using a miniaturized two-photon microscope (Zong et al., 2017). The newly developed microscope weighs 2.4 grams and allows recordings of GCaMP6-labelled cells in layer 2/3 of MEC via a compound implant consisting of a gradient refractive index (GRIN) lens and a micro prism implanted in between MEC and the cerebellum. With a 410x410 µm field of view, it allowed us to record simultaneously from several hundred cells in MEC labelled with genetically encoded calcium indicators in animals moving around in a 80x80 cm large open field. The resolution of the two-photon system allowed us to obtain recordings from cellular compartments as well as whole populations of neurons comparable to state-of-the-art benchtop microscopes. Miniaturized two-photon microscopy therefore enables unprecedented insights into the anatomical and functional network architecture of spatially modulated cell types in MEC and other brain regions.

Disclosures: H.A. Obenhaus: None. **T. Rose:** None. **W. Zong:** None. **A. Tsao:** None. **F. Donato:** None. **Ø.A. Høydal:** None. **P.M. Goltstein:** None. **M. Moser:** None. **L. Chen:** None. **H. Cheng:** None. **E.I. Moser:** None. **T. Bonhoeffer:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.07/EEE24

Topic: H.01. Animal Cognition and Behavior

Support: Argentina Science Ministry Grant PICT-2015-1273 to EK
European Research Council (Advanced Invesatigator Grant to EIM)
Research Council of Norway (Centre of Neural Computation)
Kavli Foundation

Title: Positive acceleration selectively controls theta frequency in the hippocampus and entorhinal cortex

Authors: *E. KROPFF CAUSA[1,2], J. E. CARMICHAEL[3], M.-B. MOSER[2], E. I. MOSER[2]
[1]Leloir Inst. - IIBBA - CONICET, Buenos Aires, Argentina; [2]Kavli Inst. Systems Neurosci, Trondheim, Norway; [3]Psychology and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Local field potential oscillations provide clues to understand the dynamics of large populations of neurons. In rats, the theta rhythm organizes neural activity across brain structures including the hippocampus and entorhinal cortex. Recent evidence points to a role of the theta cycle in packing together related information to produce an epoch of local computation. An additional role in spatial navigation is supported by decades of research reporting that theta frequency encodes running speed linearly, so that displacement can be obtained through theta frequency integration. Here we show, however, that this relationship is an artifact caused by the fact that, until the recent introduction of the bottomless car paradigm, the speed and acceleration of rats could not be systematically disentangled. Our results indicate that theta frequency is linearly related to positive acceleration alone, and not modulated by negative acceleration or speed (Kropff et al., SfN 2017). The rhythmic spiking of neurons follows a similar pattern, implying that both theta frequency and rhythmic spiking are nonholonomic and thus non-univocally related to displacement or any other kinematic variable. This control of theta frequency by acceleration does not require visual or motor cues, and is independent of phase precession-related variations of intrinsic firing frequency. Our results suggest that variations in theta frequency reflect a temporally precise mechanism for speeding up computations in the entorhinal-hippocampal circuits. We extend previous reports by speculating on the purpose of frequency increase. The entorhinal path integrator presumably uses information about speed but not about acceleration, as suggested by failed attempts to find acceleration-coding cells. During acceleration episodes, it should make errors in the estimation of the rat's trajectory, causing an alteration in grid spacing, as suggested by preliminary evidence that we here provide and discuss for the first time. Performing a greater number of shorter computational steps during these

acceleration episodes might help the system to improve statistics on one hand and to reduce the magnitude of these errors by reducing the temporal integration window on the other.

Disclosures: E. Kropff Causa: None. **J.E. Carmichael:** None. **M. Moser:** None. **E.I. Moser:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.08/EEE25

Topic: H.01. Animal Cognition and Behavior

Support: Kavli Foundation
Centre of Excellence grant from Research Council of Norway (Centre for Neural Computation)

Title: Grid cell formation and early postnatal experience

Authors: *I. U. KRUGE, T. WAAGA, T. WERNLE, E. I. MOSER, M.-B. MOSER
Kavli Inst. for Systems Neurosci., NTNU, Trondheim, Norway

Abstract: The medial entorhinal cortex (MEC) contains functionally specific cell classes that dynamically represent an animal´s location. A key cell type is the grid cell, whose receptive fields tile the environment in a strikingly hexagonal fashion. A central question is whether the emergence of this pattern reflects maturational processes, or whether it is shaped also by early postnatal experience. Whereas place, head direction and border cells have adult-like features when rat pups leave the nest for the first time, grid cells continue to develop for another two weeks (Langston et al. and Wills et al., Science 2011). To determine whether the extended maturation of grid cells makes them more sensitive to spatial experience, we raised 7 male or female rats for the first months of life in opaque spherical homes (Kruge et al., SfN 2016). These environments deprived the rats of opportunities to anchor representations to borders. Control animals were raised in opaque cubical boxes (n=4), or in transparent enriched environments (n=4). At mean age 13-16 weeks, animals were implanted with tetrodes in MEC. After recovery in the home environment, each animal was briefly taken out and tested for the first time in an open square food-foraging box. Testing was repeated on 2-7 consecutive days. In sphere-raised animals, the final analyses show that the symmetric, hexagonal firing pattern of grid cells was nearly absent during the first trial in the open square (only 6% grid cells). Rats raised in cubical cages displayed strong periodic firing from the onset (15% grid cells), indistinguishable from that of rats raised in enriched environments (15% grid cells). However, after repeated exploration of the open square, periodic grid patterns appeared also in sphere-raised animals (25% grid cells), suggesting that the initial deficit can be overcome. In the present report, we examine the

effect of timing of the geometric deprivation. The effect of rearing environment was age-specific. Adult rats (n=4) moved from enriched to spherical environments for minimum eight weeks showed no subsequent disruption in grid patterns (17% grid cells). Altogether, our results suggest (i) that a minimum of experience with geometric boundaries, at young age, is required for stable grid patterns to be formed rapidly in new environments, (ii) that the effect of restricted spatial experience can be overcome with relatively short training, pointing to a strong role for maturational processes, and (iii) that there is a sensitive period for experience-related effects on grid cell formation, where exposure to environmental boundaries is required for the ability to rapidly form grid patterns only at a young age.

Disclosures: I.U. Kruge: None. **T. Waaga:** None. **T. Wernle:** None. **E.I. Moser:** None. **M. Moser:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.09/EEE26

Topic: H.01. Animal Cognition and Behavior

Support: ERC grant 338865
European Commission 600725
Research Council of Norway grant 226003
Centre of Excellence scheme and the National Infrastructure Scheme of the Research Council of Norway grants 223262 and 197467

Title: Correlation structure of grid cells is preserved during sleep

Authors: *R. GARDNER[1], L. LU[2], T. WERNLE[3], M.-B. MOSER[4], E. I. MOSER[4]
[1]Kavli Inst. for Systems Neurosci., Trondheim, Norway; [2]Baylor Col. of Med., Houston, TX; [3]Kavli Inst. for Systems Neuroscience/Cnc, Trondheim, Norway; [4]Kavli Inst. Systems Neurosci, Trondheim, Norway

Abstract: The periodic spatial receptive fields of grid cells in the medial entorhinal cortex (MEC) are hypothesized to provide a universal coordinate system for physical space. The mechanisms that generate grid patterns are unknown, but the continuous attractor family of models is noteworthy since it predicts several essential features of grid cells - particularly, modular organization and invariant spatial relationships between grid cells within a module. Crucially, continuous attractor models rely on patterned recurrent connectivity in which cells with similar receptive fields are preferentially connected. We predicted that such a connectivity scheme would give rise to population activity patterns which persisted beyond navigational periods. We identified sleep as an ideal state in which to probe for signatures of continuous-

attractor-like connectivity, due to the absence of environmental influences on MEC network activity.
We recorded from MEC grid (n = 138), head-direction (HD, n = 95) and conjunctive grid-HD (n = 39) cells in adult male rats (n = 7), during open-field foraging (RUN), slow-wave sleep (SWS) and REM. We calculated functional connectivity (FC) between co-recorded cell pairs by fitting a generalized linear model (GLM) to the cells' spike rates, including the global population rate as a covariate. This allowed us to estimate FC between cell pairs, independently of global rate fluctuations.
The spatial phase offset of grid-cell pairs within a module was negatively correlated with the cell pairs' FC during SWS and REM sleep: cell pairs with small phase offsets showed positive FC, while cells with large phase offsets showed negative FC. Strong FC was not seen between grid cells from different modules. Additionally, HD phase offset in pairs of grid-HD and pure HD cells was negatively correlated with FC during sleep. We hypothesized, based on the preservation of MEC spiking correlations, that a latent grid signal persists within grid-cell population states. By modelling the latent grid signal as a random-walk process, we estimated the grid drift rate that best explained the FC temporal dynamics. We observed a 4-5-fold acceleration of the estimated grid drift rate in SWS relative to RUN. Furthermore, the relationship between grid scale and drift rate during RUN was lost during SWS.
In summary, we find a fixed, modular correlation structure in MEC that spans arousal states, as would be expected in a continuous-attractor-type network. Further investigations may elucidate the brain areas and cell types participating in grid module networks - particularly CA1 place cells, which provide an essential input to grid cells in some continuous attractor models.

Disclosures: R. Gardner: None. **L. Lu:** None. **T. Wernle:** None. **M. Moser:** None. **E.I. Moser:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.10/FFF1

Topic: H.01. Animal Cognition and Behavior

Support: ERC grant 338865
European Commission 600725
Research Council of Norway grant 226003
Centre of Excellence scheme and the National Infrastructure Scheme of the Research Council of Norway grants 223262 and 197467

Title: Theta-phase dynamics of retrospective and prospective positions signals in medial entorhinal cortex

Authors: *A. Z. VOLLAN, R. J. GARDNER, M. B. MOSER, E. I. MOSER
Fac. Of Med. and Hlth. Sciences, NTNU, Kavli Inst. For Systems Neurosci., Trondheim, Norway

Abstract: Cells in the rodent hippocampus (HC) and medial entorhinal cortex (MEC) are characterized by their sharp spatial receptive fields during navigational tasks. However, there is evidence that HC and MEC cells do not merely signal the animal's current location, but also inform about locations in the near past and future. Theta phase precession (seen in HC place cells and MEC layer II grid cells) demonstrates that individual units' spatial receptive fields change position as a function of spike theta phase (O'Keefe & Recce, 1993; Hafting et al., 2008). Furthermore, HC place-cell ensemble recordings have suggested that place field position shifts are coherent, representing trajectories that move forward from the animal's present position each theta cycle (Foster & Wilson, 2007; Feng et al., 2014; Sanders et al., 2015). This phenomenon, typically called "theta sequences", "look-ahead" or "mind-travel" has been hypothesized to support alternating encoding and retrieval epochs (Hasselmo, 2014) and goal-directed route planning (Wikenheiser & Redish, 2015), and has been hypothesized to be driven by the MEC grid-cell network (Sanders et al., 2015). However, the prevalence and ensemble-level coherence of retrospective/prospective signalling in MEC is poorly understood.
To investigate the representation of past and future position in MEC, we analysed recordings of grid cells (n = 813) from adult male rats (n = 16) while the animals foraged in an open field arena. We systematically shifted the locations of spikes retrospectively and prospectively in space, using the rat's head direction to determine the shift direction. We measured each cell's prospective/retrospective (P/R) bias by finding the position shift that maximized its spatial information. We observed a continuum of P/R biases among the population of grid cells, which was strongly linked to the cells' theta phase preference: trough-locked cells were more prospective in their signalling, while peak-locked cells were more retrospective. This relationship supports the hypothesis that individual cells' P/R representations are dictated by an underlying P/R network state. Furthermore, we observed more burst-firing in prospective cells than in retrospective cells, suggesting that anatomical cell types are differentially involved in P/R signalling. We are presently employing large-scale ensemble recordings in MEC to investigate how P/R signals are coordinated within/between grid modules and anatomical layers.

Disclosures: A.Z. Vollan: None. **R.J. Gardner:** None. **M.B. Moser:** None. **E.I. Moser:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.11/FFF2

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH097130-05
Kavli Foundation, the Centre of Excellence scheme of the Research Council of Norway – Centre for Biology of Memory and Centre for Neural Computation, The Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits
National Infrastructure scheme of the Research Council of Norway – NORBRAIN

Title: The effect of recent experience on hippocampal remapping and spatial memory impairment

Authors: *V. A. KVEIM, B. R. KANTER, C. LYKKEN, C. G. KENTROS
Kavli Inst., Trondheim, Norway

Abstract: Hippocampal place cells are thought to support the spatial component of episodic memory. Each cell is active within a particular place in an environment (place field), and this representation can be stable for many days. When an animal enters a distinct environment, however, place cells remap (change their firing rate and/or location) to form an orthogonal spatial representation. Although previous work has established a link between remapping and memory impairment, task performance can be preserved following extensive remapping under some conditions (Jeffery et al., 2003). Remapping is typically caused by switching contexts or altering sensory cues, but we recently reported a novel technique to induce remapping without any changes to the environment (Kanter et al., 2017). To do this, we used transgenic mice expressing the hM3 DREADD (Designer Receptor Exclusively Activated by Designer Drugs) in a subset of stellate cells in medial entorhinal cortex (MEC) layer II, the main spatial input to the hippocampus. Injection of the designer ligand clozapine-N-oxide (CNO) depolarized MECII neurons and elicited remapping of CA1 place cells in a stable open field environment. In a separate group of animals, the same manipulation impaired performance in the Morris water maze. Since animals were not recorded while performing a spatial task, it is still unknown whether remapping is the primary cause of this memory impairment. To directly address this question, we recorded place cells while well-trained animals performed a hippocampal-dependent Y-maze task following depolarization of MECII neurons. Spatial memory was impaired in this task as well if there was a 24-hour delay between the test session and the previous training session, but not if the delay was only 30 minutes. Surprisingly, we observed extensive remapping of CA1 place cells regardless of the timing, which raises the question of why performance differed between the two protocols. One possibility is that the hippocampal map exhibits hysteresis after a training session, thereby enabling a smooth transition between place cell representations. Interestingly, the hippocampal representation was biased toward task-relevant locations of the maze (decision and reward) in both training and test sessions, and task performance increased both within a test session and between consecutive test sessions. Taken together, these findings suggest that animals can rapidly learn to use a new hippocampal map to guide a previously learned behavior.

Disclosures: V.A. Kveim: None. **B.R. Kanter:** None. **C. Lykken:** None. **C.G. Kentros:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.12/FFF3

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH104384

Title: Optical stimulation of the pathway from the basolateral amygdala to the medial entorhinal cortex in rats enhances retention of spatial learning

Authors: *K. L. WAHLSTROM[1], R. T. LALUMIERE[2]
[2]Dept. of Psychological and Brain Sci., [1]Univ. of Iowa, Iowa City, IA

Abstract: Previous work on multiple memory systems suggests that spatial learning is mediated by hippocampus-based systems and that the basolateral amygdala (BLA) modulates the consolidation for this type of learning. The medial entorhinal cortex (mEC) is a critical region in the hippocampus-based system for processing spatial information and, as an efferent target of the BLA, is the likely mechanism by which the BLA influences spatial learning. Therefore, the present study examined whether optically stimulating activity in the BLA-mEC pathway alters the consolidation of spatial learning. Previous studies also suggest that hippocampus-based and caudate-based systems compete in the consolidation of spatial and cued-response memory, respectively. Therefore, this study also examined whether optically stimulating the BLA-mEC pathway alters the consolidation of cued-response learning. To address these questions, the BLA of male Sprague-Dawley rats were transduced to express ChR2(E123A), and fiber optic probes were implanted in the mEC to provide illumination of BLA axons. A Barnes maze was used to assess learning. During the training trials, the escape port of the maze was either located in the same position for each trial (spatial) or was marked with a distinct cue immediately above it, and the port and cue were moved in unison to a different cardinal direction for each trial (cued-response). Rats were given consecutive training trials on either task, followed immediately by 15 min of optical stimulation (8 or 40 Hz) of the BLA-mEC pathway. Rats were returned to the Barnes maze 2 d later for a single retention test. Rats that received 8 Hz but not 40 Hz optical stimulation of the BLA-mEC pathway following spatial and cued-response training had enhanced and impaired retention, respectively. These findings are consistent with the hypothesis that the neural systems mediating these two types of learning compete with one another. A follow-up study was conducted to examine ARC (activity-regulated cytoskeleton-associated protein), a plasticity-associated protein implicated in hippocampal-dependent learning and memory. Male and female Sprague-Dawley rats were trained on the spatial or cued-response version of the Barnes maze, and were sacrificed 1 h after the start of training. Brains were removed and flash-frozen and tissue punches were collected for ARC protein analysis. Western

blot was used to determine the density of ARC protein in the dorsal hippocampus. Results revealed that there were significantly higher levels of ARC in the dorsal hippocampus of male and female rats that were trained on the spatial task compared to both the cued task and a no-training control group.

Disclosures: K.L. Wahlstrom: None. **R.T. LaLumiere:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.13/FFF4

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Fellowship 110257/Z/15/Z

Title: Factoring space and time in the hippocampal-entorhinal system

Authors: *D. MCNAMEE[1,2], K. L. STACHENFELD[4,5], M. M. BOTVINICK[3,5], S. GERSHMAN[6]
[1]Computat. and Biol. Learning Lab., Univ. of Cambridge, Cambridge, United Kingdom; [2]Inst. of Neurol., [3]Gatsby Computat. Neurosci. Unit, Univ. Col. London, London, United Kingdom; [4]Neurosci., Princeton Neurosci. Inst., Princeton, NJ; [5]DeepMind, London, United Kingdom; [6]Dept. of Psychology, Harvard Univ., Cambridge, MA

Abstract: A key tenet of hierarchical reinforcement learning (HRL) is the relevance of different levels of temporal abstraction at different stages of learning and planning. When planning hierarchically, the brain should be able to flexibly specify the resolution of its state representation. Given that the hippocampus and entorhinal cortex are thought to be important brain areas for representing state, we developed a model of the hippocampal-entorhinal circuit and investigated whether the temporal resolution of state can be modulated and adapted for diverse cognitive functions.
Building on work describing grid cells as encoding eigenvectors of the environment transition matrix (Stachenfeld et al, 2017), we show how such entorhinal representations can be flexibly adapted to timescales of interest. This type of grid code “factors” the representation of time and position within a task such that a linear readout of a position-sensitive grid population and a distinct neural population encoding time predicts position at the encoded timepoint. This mechanism can be applied forward in time for prospective planning or backwards in time in order to flexibly modulate the temporal window of credit assignment during learning. In the context of HRL, if the time-coding cells encode a timepoint far into the future then a single circuit iteration outputs an estimate of the stationary state distribution which reflects the hierarchical structure of the environment. This representation can then be utilized as a pseudo-

reward “map”. According to this mechanism, higher pseudo-rewards are attributed to, for example, topological junctions which have previously been proposed as natural subgoals for HRL.
Furthermore, the recurrent nature of the entorhinal-hippocampal circuit has a natural correspondence in our model which supports the “roll-out” of place cell activation sequences. With simulations, we show how the time-coding population can dynamically scale the temporal coarseness of sequential position sampling, leading to non-local “jumps”. These jumps can interleave global position shifts with local searches and selectively visit natural subgoals in accordance with the multi-scale structure of the environment. Thus, this dynamical mode of our model can support the retrieval of states in an order distinct from that in which they were experienced but which is optimized for planning. In addition, our model replicates several empirical phenomena influenced by environment topology, such as the rapid sweeping of sequential place cell activity to and from maze junctions, a behavioral bias toward traversing environment boundaries, and the Levy walk statistics of large-scale foraging.

Disclosures: D. McNamee: None. **K.L. Stachenfeld:** None. **M.M. Botvinick:** None. **S. Gershman:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.14/FFF5

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R37NS081242

Title: A topographical map of space: Micro-organization of grid cells in the medial entorhinal cortex

Authors: *Y. GU[1], S. LEWALLEN[1,2], A. A. KINKHABWALA[1,3], C. DOMNISORU[1,2], K. YOON[4,5], J. L. GAUTHIER[1], I. R. FIETE[5], D. W. TANK[1]
[1]Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Harvard Univ., Cambridge, MA; [3]Biol. and Biol. Engin., Caltech, Pasadena, CA; [4]Dept. of Neurosci., Baylor Col. of Med., Houston, TX; [5]Ctr. for Learning and Memory, UT Austin, Austin, TX

Abstract: Topographical maps are intriguing features of brain structure, in which the anatomical organization of neurons corresponds to specific properties of encoded variables. Although it is still unclear how these maps relate to functional mechanisms, they have been observed in many sensory and motor systems, such as the retinotopic map in primary visual cortex and the somatotopic map in somatosensory cortex. In contrast, topographical maps for cognitive variables are rarely reported.

Here we report a fine-scale topographical map in a high-level cognitive cortical circuit in the rodent brain. Using cellular-resolution two-photon calcium imaging during virtual navigation, we investigated the relationship between the anatomical organization and functional properties of grid cells, which represent a cognitive code for location during spatial navigation. We found a substantial degree of grid cell micro-organization in layer 2 of mouse medial entorhinal cortex. First, grid cells and modules all clustered anatomically. In addition, grid cells within the same module are topographically arranged. In the local neighborhood, grid cells are spatially organized according to the relative offsets of their spatial tuning phases, and exhibit a pattern in which anatomically nearby grid cells have more similar phases than distal grid cells. On a larger spatial scale, grid cell phases repeat their local pattern to form a noisy two-dimensional lattice structure that tiles the anatomical surface of the cortex. This map of grid cells contributes to a foundation for evaluating circuit models of the grid cell network, and is consistent with continuous attractor models as the mechanism of grid formation. The relationship between the anatomical distribution of grid cells and their function in mouse MEC demonstrates how topography and function can be intimately related in neural circuits underlying cognitive variables.

Disclosures: S. Lewallen: None. **A.A. Kinkhabwala:** None. **C. Domnisoru:** None. **K. Yoon:** None. **J.L. Gauthier:** None. **I.R. Fiete:** None. **D.W. Tank:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.15/FFF6

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust 536266

Title: Relatively specific inhibition of grid cells by somatostatin positive interneurons in medial entorhinal cortex

Authors: *R. M. HAYMAN[1], N. BURGESS[2]
[1]Inst. of Neurol., London, United Kingdom; [2]UCL, London, United Kingdom

Abstract: The role, if any, of GABAergic interneurons in generation of the periodic grid code found in medial entorhinal cortex (mEC) is currently unknown, although continuous attractor models predict a specific pattern of recurrent inhibition (1). Exciting parvalbumin positive interneurons has been shown to inhibit all major cell types in the mEC (2), but we wondered whether exciting the next most common, (somatostatin positive, SST+) interneurons would have a more specific effect.
To assess this we used a combination of optogenetics and tetrode recordings in SST+-Cre mice.

We found that increasing the activity of SST+ cells strongly inhibited grid cells, had a mild effect on speed cells and theta-modulated cells and little to no effect on either border or head-direction cells. The latency of the effect on grid cells following SST+ cell activation strongly suggests a mono-synaptic connection between SST+ interneurons and grid cells and a longer, possibly multi-synaptic, latency to speed and theta-modulated cells. During the period of optogenetic stimulation the properties of grid cells were not noticeably affected; spatial phase, wavelength and orientation remained the same as during baseline but with a reduced firing rate. Similarly the depth of theta modulation was not significantly affected and neither was a measure of a cells speed tuning. The few identified SST+ cells (those with a short enough latency following light onset) had patchy spatial receptive fields and were weakly modulated by the animals speed. Our findings indicate a relatively specific role of SST+ interneurons in the inhibition of grid cell firing.
1. Burak & Fiete 2009 PLoS Comp Biol
2. Buetfering, Allen, Monyer 2014 Nat Neuro

Disclosures: R.M. Hayman: None. **N. Burgess:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.16/FFF7

Topic: H.01. Animal Cognition and Behavior

Support: ERC Advance grant NEUROMEM
Wellcome Trust

Title: A computational model of visual recognition memory via grid cells

Authors: *A. BICANSKI, N. BURGESS
Inst. of Cognitive Neurosci., UCL, London, United Kingdom

Abstract: Grid cells represent environmental location and likely underlie path integration, imagined movement, and the computation of movement vectors during spatial navigation. However, recent results suggest that some entorhinal cells can also exhibit grid-like firing patterns in response to saccades, i.e. in visual space. Here we propose a mechanistic model of object, face, and scene recognition that makes use of grid cell representations to encode the translation vectors between salient features. Drawing parallels to active exploration in spatial tasks, we propose that visually driven grid cells calculate saccade vectors moving from one salient feature of an image to the expected location of the next. A sequence of saccade vectors which visits salient features of an image is identified with recognition of the layout of the image (i.e., going beyond recognition of the individual features). The proposed model provides an

explicit neural mechanism underlying the long-held view that directed saccade vectors support hypothesis-driven, constructive perception and recognition, and the first quantitative explanation of a possible role for grid cells in visual processing. The variance of activity across grid cells sampled along saccade trajectories varies with saccade direction with 6-fold symmetry, which may explain recently reported fMRI findings. The model also suggests a functional explanation for why some kinds of visual memory involve the medial temporal lobe. The mechanism is robust with regards to visual occlusions, is invariant with respect to the apparent size and position of the stimulus in the visual field, and suggests a large number of experimental predictions.

Disclosures: A. Bicanski: None. **N. Burgess:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.17/FFF8

Topic: H.01. Animal Cognition and Behavior

Support: Welcome Trust grant 509999

Title: Entorhinal neurons exhibit cue locking in rodent VR

Authors: *G. CASALI, C. DOWELL, S. SHIPLEY, R. HAYMAN, C. BARRY
Cell and developmental biology, UCL, London, United Kingdom

Abstract: The spatially regular firing pattern of rodent medial entorhinal (mEC) grid cells is hypothesized to function as a spatial metric relevant for navigation. The exact computations that generate grid-patterns are unknown but experimental evidence suggests that both self-motion integration and environmental cues contribute to the formation and stability of grid cell firing. The development of the virtual reality (VR) for head-fixed mice confers a number of experimental advantages and has becoming increasingly popular as a method for investigating spatially-selective cells. Recent work conducted in 1D virtual linear tracks showed that cells in MEC fire at regular intervals in virtual space analogous to grid cells in real linear tracks. We recorded from mEC as mice traversed virtual tracks, identifying a population of neurons with firing fields modulated by regularly repeating visual cues - thus resembling regular grid cell firing patterns. However, in the open field these cells lacked the six-fold periodicity typical of grid cells, exhibiting weakly spatial firing. In the virtual environments the frequency of their firing-pattern precisely corresponded to visual features in the VR, indicating that their apparently grid-like activity was likely an artefact induced by composite responses to visual cues. In light of these results we highlight the importance of controlling the periodicity of the visual cues in VR and the necessity of open field recordings for the accurate characterisation of mEC cells.

Disclosures: G. Casali: None. **C. Dowell:** None. **S. Shipley:** None. **R. Hayman:** None. **C. Barry:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.18/FFF9

Topic: H.01. Animal Cognition and Behavior

Support: Sir Henry Dale Wellcome Fellowship
UCL Excellence Felowship
Medical Research Council

Title: Relationship between place cell recruitment and the spatial scale of open-field environments revealed using a novel scalable recording apparatus

Authors: *S. TANNI, C. BARRY
Cell and Developmental Biol. Dept., Univ. Col. London, London, United Kingdom

Abstract: The representation of space in hippocampal circuits and how it supports navigation has been studied extensively in minimalistic experimental environments. However, our understanding of how hippocampal networks encode large and complex spaces is limited. The spatial scale of experiments in freely moving rodents is in part limited by lack of technological solutions for this purpose. We developed an open-source, modular, scalable system to control interactive spatial tasks in large-scale environments. Thus, allowing us to perform extremely long duration electrophysiological recordings in which animals explore large spaces. Prior work, conducted on linear tracks, indicated that place cell recruitment followed a logarithmic relationship over scale [1]. To determine if a similar pattern was evident in the open-field, we performed recordings in environments of variable sizes up to 9 m^2, using our novel control system.
Open Ephys recording system was used for electrophysiological recordings, while online position tracking and reward mechanisms utilized multiple Raspberry Pi units that were controlled wirelessly by a Linux based PC. Two types of reward mechanisms, scattered pellets and localized milk drops, ensure sufficient coverage of open-field for studying spatial cells as well as goal orientated navigational behaviour.
Place cells were recorded in male Lister Hooded rats during foraging in distinct environments of different sizes. We found a non-linear relationship between the size of the open-field environment and the properties of place fields. Specifically, the distribution of place fields relative to the environmental boundaries depended on the size of the environment. These results show the importance of large scale open-field recordings for understanding the properties of

hippocampal circuits during real world navigation.
1. Rich, P. D., et al., *Science.* 345, 814-817 (2014)

Disclosures: S. Tanni: None. **C. Barry:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.19/FFF10

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome
European Union's Horizon 2020 research and innovation programme (grant agreement No. 720270, HBP SGA1)
Biotechnology and Biological Sciences Research Council
European Research Council
China Scholarship Council

Title: Absence of visual input affects place and grid cell activity

Authors: *Y. LU, G. CHEN, N. BURGESS, T. WILLS, F. CACUCCI
Univ. Col. London, London, United Kingdom

Abstract: It is known that visual cues can exert control over the spatial firing fields of place and grid cells. However, it is still an open question whether vision affects grid and place fields independently or not and whether that influence is uniform across the whole environment. Previous studies have shown that, in mice, grid cells lose their hexagonal firing regularity in familiar environments when the lights are turned off (see 1). To further explore the relationship between grid cell and place cell firing, it is interesting to know how place cell firing in mice responds to absence of visual input. We recorded place and grid cells concurrently while mice performed random foraging in the dark followed by a control trial in the light. Our results demonstrated that the spatial selectivity of place cell firing was largely preserved while their spatial tuning stability was decreased. Specifically, some place cells fired at a lower rate and some had firing fields that shifted in location. The spatial regularity of grid cell firing patterns was also disrupted. Moreover, place and grid fields closer to the walls showed better stability compared to fields away from the environmental boundaries. 1) Chen, Manson, Cacucci, Wills. Absence of Visual Input Results in the Disruption of Grid Cell Firing in the Mouse. Curr. Biol. 2016; 26:2335-2342

Disclosures: Y. Lu: None. **G. Chen:** None. **N. Burgess:** None. **T. Wills:** None. **F. Cacucci:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.20/FFF11

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome
European Union's Horizon 2020 research and innovation programme (grant agreement No. 720270, HBP SGA1)
Biotechnology and Biological Sciences Research Council
European Research Council
China Scholarship Council
Medical Research Council

Title: 2-photon imaging of mouse hippocampus during virtual navigation of open arenas

Authors: *G. CHEN[1], R. M. HAYMAN[2], Y. LU[3], J. KING[4], T. KECK[5], F. CACUCCI[5], N. BURGESS[6]
[1]Univ. Col. of London, London, United Kingdom; [2]Inst. of Neurol., London, United Kingdom; [3]UCL, london, United Kingdom; [4]CEHP, [5]NPP, [6]UCL, London, United Kingdom

Abstract: We present a mouse virtual reality (VR) system which restrains head-movements to horizontal rotations and is compatible with multi-photon imaging. We show that this system allows expression of the spatial navigational behaviour (returning to an unmarked goal location) and the spatial neuronal firing patterns characteristic of real open arenas, including place, grid and head-direction cells. Using genetically encoded GCaMP6f mice we demonstrate stable 2-photon fluorescence imaging of neuronal activity of large populations in hippocampal area CA1. Imaging during active spatial navigation in open environments demonstrates the spatial activity patterns of place cells, enabled by software developed to un-rotate the images acquired.1) Chen, King, Lu, Cacucci, Burgess, bioRxiv 2018 doi: https://doi.org/10.1101/246744

Disclosures: G. Chen: None. **R.M. Hayman:** None. **Y. Lu:** None. **J. King:** None. **T. Keck:** None. **F. Cacucci:** None. **N. Burgess:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.21/FFF12

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust
European Research Council
European Union's Horizon 2020 Research and Innovation Program, Grant Agreement #720270

Title: Grid cell phase coding does not require constant rhythmicity

Authors: *D. BUSH, N. BURGESS
UCL Inst. of Cognitive Neurosci., London, United Kingdom

Abstract: Phase coding - the encoding of information in spike phase relative to an ongoing oscillation in the local field potential (LFP) - offers numerous theoretical advantages over an equivalent firing rate code. Empirical studies have provided evidence for phase coding across multiple species and cortical regions. For example, grid cells in rodent medial entorhinal cortex, which are characterised by a regular triangular array of spatial firing fields, exhibit 'theta phase precession' - spiking at progressively earlier phases of the 5-11Hz theta oscillation as each firing field is traversed. It has often been assumed that such phase coding relies on a high amplitude baseline oscillation with relatively constant (theta) frequency. However, recent data demonstrate that grid cells in both bats and humans exist in the absence of a constant frequency oscillation in either the spike train or LFP, calling into question the existence of phase coding in these species. We show that, if the intrinsic firing frequency of grid cells varies relative to a dynamically changing baseline frequency according to movement velocity, then grid cell firing patterns can efficiently multiplex information about location, running speed, movement direction and a fourth variable such as anxiety. We simulate a population of grid cells that exhibit phase precession against a baseline oscillation with highly variable frequency recorded from depth electrodes in human hippocampus. We then show that it is possible to accurately decode location from population firing rates, consistent with previous studies; movement direction from firing phase, analogous to experimentally observed 'theta sweeps' of activity along the animal's current trajectory; running speed from mean firing rates; and anxiety from the baseline oscillation frequency. In addition, we investigate how firing phase might be used to reduce errors in decoded location that arise from stable differences in in-field firing rates. Finally, we describe analytical methods that can identify phase coding in the absence of a constant frequency oscillation, as in single unit recordings from the bat or human brain.

Disclosures: D. Bush: None. **N. Burgess:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.22/FFF13

Topic: H.01. Animal Cognition and Behavior

Title: Predictive coding in the bat hippocampus

Authors: *D. OMER, N. ULANOVSKY
Neurobio., Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Hippocampal place cells represent the current position of the animal - and recent studies in bats and rats found that the position of other animals is represented by hippocampal 'social place-cells'. Previous studies in rodents showed that CA1 neurons also exhibit prospective coding, anticipating the animal's choice behavior. In bats, little is known about how the hippocampus represents future spatial trajectories. To examine this question we used a delayed match-to-place task which was used previously to demonstrate social place-cells: In each trial, one bat ('observer') had to observe and remember the flight-trajectory of the other bat ('demonstrator'). After a short delay, the observer had to imitate the demonstrator's flight to receive a reward. We recorded hippocampal dorsal-CA1 neurons in the observer. In this study we focused on the delay period between the return of the demonstrator and the takeoff of the observer. Our preliminary results suggest that firing patterns of CA1 neurons in the observer bat are anticipating his flight trajectory a long time before his takeoff - while the two bats are stationary on the same start-ball.

Disclosures: N. Ulanovsky: None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.23/FFF14

Topic: H.01. Animal Cognition and Behavior

Title: Representation of 3D space in the entorhinal cortex of flying bats

Authors: *G. GINOSAR, A. FINKELSTEIN, L. LAS, N. ULANOVSKY
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Grid cells recorded from animals exploring 2D planes, fire in an hexagonal pattern across the environment. However, many animals navigate through 3D space, but no studies have characterized the 3D volumetric firing of grid cells. Here, we trained Egyptian fruit bats (*Rousettus aegyptiacus*) to fly in a large room, while we wirelessly recorded single-neuron activity in medial entorhinal cortex (MEC). Our results revealed structured firing in the 3D firing-rate maps, with multiple firing-fields. The spacing between firing-fields was more variable than in perfect synthetic 3D lattices, but was less variable than shuffled data: about 20% of the multi-field neurons were 3D grid cells, exhibiting a significantly fixed distance scale. This result supports a distance-coding function for grid cells. The 3D grid cells seemed to form a functional continuum - in terms of spatial structure - with the less structured multi-field neurons. The population of multi-field cells in bat MEC exhibited an anatomical gradient of spatial scales along the dorso-ventral axis of MEC, with inter-field spacing increasing more ventrally - similar to what is seen in rodents in 2D. We also found a number of other 3D spatial cell types in bat MEC, including (i) 3D border cells, (ii) 3D head-direction cells, and (iii) a new class of MEC neurons that fired selectively near specific landing-balls - but not near other balls. Taken together, these data suggest a rich 3D spatial representation in the MEC of flying bats - including coding of 3D space by grid cells, coding of 3D geometry by border cells, as well as object-related coding in the bat MEC.

Disclosures: G. Ginosar: None. **A. Finkelstein:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

689. Spatial Navigation: Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 689.24/FFF15

Topic: H.01. Animal Cognition and Behavior

Title: Representation of large-scale spaces in the hippocampus of flying bats

Authors: *T. ELIAV, L. LAS, N. ULANOVSKY
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Most animals navigate daily over distances spanning from hundreds of meters to many kilometers. However, over the last forty years, hippocampal research focused on spatial representations in small laboratory environments. Nothing is known about hippocampal neural codes for large spatial scales - the scales of natural navigation of rodents, bats and other mammals. Here we addressed this question for the first time, by developing a unique setup - including a very large environment with an ethologically-relevant spatial scale. We studied Egyptian fruit bats - flying mammals that are excellent navigators over large scales, and which have rodent-like hippocampal spatial representations in small laboratory environments. We developed an on-board wireless neural-logging system, which allows recording single-units over

unlimited distances. We built a 200-m long tunnel where bats can fly freely; bat's position was tracked using an RF localization device that measures distances to a ground-based antenna array - yielding high accuracy of ~10-cm, much better than GPS. Bats flew back-and-forth along the tunnel, more than 100 laps per-session (>20-km total distance). Preliminary recordings from hippocampal area CA1 showed some firing properties that were similar to findings in small-scale laboratory environments, such as directionality and field-asymmetry. However, most properties were very different: (i) Individual cells exhibited multiple fields per neuron. (ii) We found very large fields in dorsal CA1 - up to 20-30 meters. (iii) A given neuron could exhibit multiscale spatial coding - with different place-fields of the same neuron having very different sizes, ranging from sub-meter to 20-30 m. These large variations in scale were unrelated to local landmarks, and could not be explained by the animal's flight speed, which was extremely stable along the tunnel - suggesting that CA1 neurons have a genuine multi-scale representation. Taken together, the firing properties of CA1 neurons in this large-scale environment suggest a representation that is very different from findings reported in the laboratory.

Disclosures: T. Eliav: None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.01/FFF16

Topic: H.01. Animal Cognition and Behavior

Title: The beneficial role of noisy inhibitory signaling in collective behavior

Authors: *H. C. BELL[1], F. D. BROCCARD[2], Y. ZHU[3], J. C. NIEH[4]
[2]Inst. for Neural Computation, [3]Computer Sci. and Engin., [4]Div. of Biol. Sciences; Section of Ecology, Behavior, and Evolution, [1]Univ. of California San Diego, La Jolla, CA

Abstract: Noise, defined as anything that interferes with the transmission, reception, or interpretation of a signal from sender to receiver during communication, is a ubiquitous feature of biological systems. Although traditionally viewed as an inevitability that systems learn to cope with, some recent findings suggest that noise can be beneficial under certain conditions - for instance, by fostering behavioral and phenotypic variability and via mechanisms such as stochastic resonance. Our work focuses on understanding the role of spontaneous (noisy) signaling in collective decision-making. Using honey bees as our model system, in conjunction with computational modeling approaches, we demonstrate that noisy inhibitory signaling in complex systems can confer an adaptive advantage under dynamic conditions. In particular, collectives implementing such noisy signals are more robust to perturbation and less likely to make Type I errors.

Disclosures: H.C. Bell: None. **F.D. Broccard:** None. **Y. Zhu:** None. **J.C. Nieh:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.02/FFF17

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Intramural Research Program (ZIAMH002887)

Title: Effect of anterior cingulate cortex lesions on social vicarious reinforcement in monkeys

Authors: *B. M. BASILE[1], J. SCHAFROTH[1], C. KARASKIEWICZ[1], S. W. CHANG[2], E. A. MURRAY[1]
[1]Lab. of Neuropsychology, Natl. Inst. of Mental Health, NIH, Bethesda, MD; [2]Yale Univ., New Haven, CT

Abstract: Humans and monkeys will sometimes work to see a conspecific get rewarded, a phenomenon called vicarious reinforcement. Behavior in vicarious reinforcement tasks and similar social decisions correlate with the activity of neurons in the anterior cingulate cortex (ACC) in monkeys and with blood oxygen-level dependent changes in the ACC in humans. These correlations suggest a critical role for the ACC in social decisions. However, some human patients with accidental damage that includes the ACC are unimpaired on a number of tasks that assess social cognition. We addressed this discrepancy by testing rhesus monkeys (*Macaca mulatta*) on a social vicarious reinforcement task before and after selective, bilateral ibotenic acid lesions of the ACC. An actor monkey sat facing a computer screen while a recipient monkey sat next to the screen facing the actor. On each trial, actors were required to fixate on a visual cue that rotated to predict one of three reward offers: juice to oneself, juice to the other monkey, or juice to neither monkey. Actors could accept the offer by making a saccade to a peripheral target or reject the offer by not making a saccade. Before surgery, all monkeys showed a moderate but reliable preference for giving juice to the other monkey over giving it to neither monkey. Unexpectedly, pupil size was wider in anticipation of the less-preferred *neither* trials than the more-preferred *other* trials, suggesting that eye movements tracked outcome valence whereas pupil size, a measure of autonomic arousal, tracked outcome salience. After surgery, both lesion and control groups maintained their social preferences to the pre-operatively learned cues. We will also discuss results from post-operative learning of novel cues. These data speak to the causal role of the primate ACC in vicarious reinforcement.

Disclosures: B.M. Basile: None. **J. Schafroth:** None. **C. Karaskiewicz:** None. **S.W. Chang:** None. **E.A. Murray:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.03/FFF18

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Intramural Research Program ZIAMH002887

Title: Effect of primate amygdala and anterior cingulate cortex lesions in viewing biologically relevant stimuli

Authors: *J. SCHAFROTH[1], B. M. BASILE[2], D. R. LUCAS, III[3], E. A. MURRAY[4]
[1]Lab. of Neuropsychology, Natl. Inst. of Hlth., Bethesda, MD; [2]Lab. of Neuropsychology, Natl. Inst. of Mental Health, NIH, Bethesda, MD; [3]NIH, Bethesda, MD; [4]Lab. of Neuropsychology, NIMH, NIH, Bethesda, MD

Abstract: Human and nonhuman primates live in complex social structures. Recent research has posited a distributed neural network, sometimes called the "social brain", that preferentially processes social information. Two brain regions implicated in social processing are the amygdala and anterior cingulate cortex (ACC). In primates, amygdala neuronal activity correlates with important aspects of hierarchical ranks, faces, and social decisions, and ACC activity correlates with aspects of observational learning and vicarious reinforcement. However, there is still a paucity of evidence about the causal roles these structures have in processing social information. In addition, the extent to which the neural correlates are due to the information being specifically social or generally biologically relevant remains unknown. Here, we evaluated if rhesus macaques (*Macaca mulatta)* with bilateral, excitotoxic, lesions of the amygdala or ACC viewed biologically relevant stimuli abnormally compared to unoperated controls. Controls (n=10) and monkeys with amygdala (n=8) or ACC (n=3) lesions viewed 15-second videos from three categories of biologically relevant stimuli: conspecifics, food, and predators. Monkeys also viewed control movies that displayed similar backgrounds without active entities and scrambled versions of all videos. We hypothesized that if the amygdala and ACC are involved in processing biologically relevant stimuli, damage to these areas would result in abnormal viewing patterns for all three classes of stimuli. Surprisingly, our preliminary analysis showed no robust effect of either lesion on viewing social videos. However, monkeys with amygdala damage spent more time viewing food videos compared to the other groups. In addition, relative to controls, both the amygdala and ACC lesion groups spent more time viewing predator videos. Both findings were driven by long fixations (>0.5 sec), suggesting attentional rather than exploratory viewing. Group differences in the spatial distribution of attention to various scene elements will also be discussed. Overall, these data provide causal evidence that the primate amygdala and ACC

contribute generally to the processing of biologically relevant stimuli as opposed to narrowly to the processing of social information.

Disclosures: J. Schafroth: None. **B.M. Basile:** None. **D.R. Lucas:** None. **E.A. Murray:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.04/FFF19

Topic: H.01. Animal Cognition and Behavior

Support: NARSAD YI Award 25066
MGH Fund for Medical Discovery
NIMH Grant MH112846
NINDS Grant NS091390

Title: Single-neuronal correlates of group behavior and reciprocity in three interacting macaques

Authors: *R. BÁEZ-MENDOZA, E. P. MASTROBATTISTA, A. J. WANG, K. HU, Z. M. WILLIAMS
Dept. of Neurosurg., Massachusetts Gen. Hospital-Harvard Med. Sch., Boston, MA

Abstract: Reciprocity is a central feature of social interaction in both humans and animals. It allows individuals to forge alliances and function within groups and is instrumental in augmenting both individual and mutual fitness. Its dysfunction is also a prominent feature of many psychiatric conditions and prominently contributes to social behavioral disorders. Yet, the precise neuronal computations that underlie reciprocity and group behavior remain poorly understood. Here, we obtained multiple-neuronal recordings in the anterior cingulate cortex (ACC) of small groups of rhesus macaques as they performed a structured reciprocity-based social task. We devised a three-agent social task in which three macaques interacted with each other over multiple rounds. The task required the monkeys to sit around a rotary table apparatus; in each trial, one individual would offer a food reward to one of the other two. Throughout sessions, individuals within groups of three could reciprocate past rewards that had been delivered to them by other group members. Based on this design, we could dissociate basic computations associated with interactive behavior, social preference, and group dynamics. Within experimental sessions, we also controlled for animal position and gaze contact between actor and potential recipients. Behaviorally, we find that the monkeys demonstrated a strategic preference for other individuals and that they favored rewarding those who reciprocated. At the neuronal-level, a distinct subpopulation of neurons tracked the reward received by other group members. However, they also maintained a representation of distinct individuals and their association with reciprocated reward. These findings reveal neurons in the primate ACC that

encode information about particular individuals, their behavior within social groups and their reciprocity. Together, they also lay the future groundwork for studying social behavior in humans and for testing neurobiology-guided clinical treatments.

Disclosures: R. Báez-Mendoza: None. **E.P. Mastrobattista:** None. **A.J. Wang:** None. **K. Hu:** None. **Z.M. Williams:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.05/FFF20

Topic: H.01. Animal Cognition and Behavior

Support: FIRB 2010

Title: Dorsal premotor neurons distinguish between self and other's future choices

Authors: *L. FERRUCCI[1], R. CIRILLO[2], E. MARCOS[2], S. FERRAINA[3], A. GENOVESIO[4]
[1]Univ. of Rome Sapienza, Roma, Italy; [2]Sapienza Univ. of Rome, Rome, Italy; [3]Sapienza Univ. Rome, Rome, Italy; [4]Sapienza Univ., Roma, Italy

Abstract: Social interaction plays a fundamental role in primate life. The premotor cortex is assumed to be involved in representing self and others' behavior since the discovery of mirror neurons in its ventral part. The dorsal premotor cortex (PMd) is tought to play a similar role, with a neural network responsible for planning and executing actions that overlaps with the network for observation of other's actions. We used a social interaction task in which two male rhesus monkeys were required to interact with a human partner, alternating their roles as actor or observer. The monkeys were trained to perform two versions of a non-match-to-goal (NMTG) task: a spatial version (S-NMTG) and an object version (O-NMTG). The rule in the two versions of the task was identical: in each trial, the monkeys were required to select the object (in O-NMTG) or the position (in S-NMTG) that did not match the one chosen in the previous trial. In both versions, the new object/location had to be chosen in order to receive a reward. During the recording sessions, monkeys interacted with a human partner in a subset of trials; in these trials, the monkey had to monitor the human partner performing the task and to observe the target chosen, in order to discard it and chose the new one in the successive trial. We recorded in the PMd the activity of 210 single cells in Monkey 1 and 118 single cells in Monkey 2, for a total of 328 neurons. We analyzed the neural activity in human and monkey trials during the delay period, since in this period there was no movement. In contrast to previous studies, we found that only a minority of the task-selective neurons (19%) exhibited congruent directional activities (mirror-like) for both one's own and other's future actions. Moreover, some neurons predicted the future response (left versus right) only during the human's performance without coding the

response during the monkey's own turn. Our results suggest that PMd could play a crucial role in social cognition. It appears that PMd is not mainly involved in mirror-like processes but that this area can contribute to distinguish between one's own and other's actions. Overall, PMd could very well play an important role during social interaction given its connectivity with other frontal areas involved in the "social network", such as lateral prefrontal cortex and supplementary motor areas.

Disclosures: L. Ferrucci: None. **R. Cirillo:** None. **E. Marcos:** None. **S. Ferraina:** None. **A. Genovesio:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.06/FFF21

Topic: H.01. Animal Cognition and Behavior

Support: Canadian Institutes of Health Research

Title: A method to analyze sociability in the common marmoset based on 3D tracking

Authors: *D. BUITRAGO-PIZA[1], G. M. PARFITT[2], B. W. CORRIGAN[3], J. C. MARTINEZ-TRUJILLO[4]
[2]Dept. of Neurosci., [1]Western Univ., London, ON, Canada; [3]Neurosci., [4]Physiol. and Pharmacol., Univ. of Western Ontario, London, ON, Canada

Abstract: Common marmosets create complex social networks within family groups, their social interactions rely greatly on visual and auditory cues, making them an ideal model of human social aspects. In this work, we sought to identify general social interest in freely moving marmosets using 3D body position and orientation in a semi naturalistic environment in the presence of social novelty. In the study, two adult marmosets were habituated for two weeks to freely move inside a plexiglass recording chamber with four vertical levels while wearing a detachable vest with affixed infrared reflective markers that allowed 6 degrees of freedom positional camera tracking (Optitrack, Natural Point Inc, USA). After two weeks, the animals became used to roam on all the 4 different levels of the chamber developing a natural preference to stay on higher levels from the ground. After the habituation period, 15 minutes sessions were recorded with a clean transparent box attached to the bottom level of the chamber. The marmosets had visual access to it at all times, 4 conditions were presented inside the box on different days: monkey dummy, same sex novel juvenile, same sex novel mature marmoset, and an empty box control. Distance from the tracked marmoset body (D) and orientation (O) relative to the box were computed and normalized to the maximal possible distance and angle respectively. An index (1-[D x O]) was used as a score of sociability. The results showed that in

both animals scores were higher when a novel mature marmoset was inside the box (n1 = 0.55, n2 = 0.52), following by juvenile inside the box (n1 = 0.46, n2 = 0.47), dummy (n1 = 0.4, n2 = 0.43) and empty box (n1 = 0.35, n2 = 0.27) respectively. Direct interactions (Di) were considered as events in which the marmoset approached the box within 5 cm distance. Di were higher for the mature marmoset than in all other conditions (n1 = 38, n2 = 14), following by juvenile (n1 = 0, n2 = 2), dummy (n1 = 0, n2 = 0) and empty box (n1 = 6, n2 = 0). Our results describe a reliable and relative unexpensive method to measure sociability in marmosets.

Disclosures: D. Buitrago-Piza: None. **G.M. Parfitt:** None. **B.W. Corrigan:** None. **J.C. Martinez-Trujillo:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.07/FFF22

Topic: H.01. Animal Cognition and Behavior

Support: Strategic Partnership Programme Grant from Science Foundation Ireland and Alkermes, Inc. (14/SPP/B3051).

Title: Evaluation of the 3-chamber sociability test in the olfactory bulbectomized (OB) rat model of depression

Authors: *K. L. MCHUGH[1,2], H. DOHERTY[1,2], P. CALCAGNO[1,2,3], M. CLARKE[1,2,3], D. EYERMAN[4], C. SANCHEZ[4], M. ROCHE[3,2], D. P. FINN[1,2], J. KELLY[1,2]
[1]Pharmacol. and Therapeut., Natl. Univ. of Ireland Galway, Galway, Ireland; [2]Galway Neurosci. Ctr. NCBES, Galway, Ireland; [3]Physiol., Natl. Univ. of Ireland, Galway, Galway, Ireland; [4]Alkermes, Inc., Waltham, Massachusetts, MA

Abstract: Introduction:
The olfactory bulbectomy (OB) rat model is a well-established model with a number of behavioural changes, some of which are attenuated by chronic antidepressant treatment. The 3-chamber sociability test evaluates rodents' ability to discriminate between an unfamiliar and a familiar rat, and has value in the context of assessing cognitive function. The objective of this study was to evaluate the 3-chamber sociability test in the OB model by examining differential housing (single versus paired), and the effect of chronic administration of the antidepressants desipramine and fluoxetine.
Methods:
Male Sprague Dawley rats (200-250g) underwent surgery (sham or OB) under isoflurane anaesthesia, or did not undergo surgery (naïve). In the single – *vs*. group-housing study, rats were singly housed or pair housed (either paired shams, paired OB, or a sham paired with an OB)

following surgery (n=8). In the antidepressant study, rats were singly housed and two weeks post-surgery rats received daily subcutaneous injections of vehicle (saline), desipramine or fluoxetine (both 10mg/kg) for two weeks (n=8). Four weeks post-surgery, rats were tested in the 3-chamber sociability test, consisting of three consecutive ten-minute time-trials; the *habituation trial* (empty arena), the *sociability trial* (novel rat vs. empty cage) and the *social preference trial* (now familiar rat vs. novel rat). Total distance moved was recorded using Ethovision® technology. The degree of habituation was calculated as the 3rd trial as a percentage of the 1st trial. Duration exploring was manually scored. Data are expressed as mean ± SEM and analysed using two-way ANOVA, followed where appropriate by *post-hoc* Student Newman-Keuls test; $p<0.05$ was deemed statistically significant.

Results: In the sociability trial, OB rats paired together, spent less time exploring the novel rat than their sham counterparts. In the social preference trial, all OB rats, regardless of housing, spent less time exploring the novel rat as well as displaying a significant habituation to the apparatus when compared to sham counterparts. Sham-operated and naïve rats behaved similarly to each other, irrespective of housing. Treatment with antidepressants did not attenuate the OB-related changes.

Conclusion: Olfactory bulbectomy causes altered social cognition with pronounced reduction in social preference and habituation to the test arena. These results add an additional behavioural alteration to the model, but one that is not altered by chronic antidepressant treatment.

Disclosures: K.L. McHugh: 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.; Alkermes, Inc.,, Science Foundation Ireland. **H. Doherty:** None. **P. Calcagno:** 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.; Alkermes, Inc.,, Science Foundation Ireland. **M. Clarke:** 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.; Alkermes, Inc.,, Science Foundation Ireland. **D. Eyerman:** 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.; Alkermes, Inc.,, Science Foundation Ireland. **C. Sanchez:** 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.; Alkermes, Inc.,, Science Foundation Ireland. **M. Roche:** 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.; Alkermes, Inc.,, Science Foundation Ireland. **D.P. Finn:** 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.; Alkermes, Inc.,, Science Foundation Ireland. **J. Kelly:** 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.; Alkermes, Inc.,, Science Foundation Ireland.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.08/FFF23

Topic: H.01. Animal Cognition and Behavior

Support: NASA Grant NNX15AC71G to CMD

Title: The medial prefrontal cortex is involved in social odor recognition memory in rats

Authors: *S. ROBINSON[1], S. J. ALDRICH[1], L. GRANATA[2], R. D. HEINZ[2], C. M. DAVIS[2]
[1]Psychology Dept. and Neurosci. Program, Hamilton Col., Clinton, NY; [2]Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: The medial prefrontal cortex (mPFC) is critical for several cognitive processes including olfactory discrimination and social cognition, but its specific role in memory processing when social cues are involved is unclear. Using a chemogenetic approach in rats, we assessed the role of the mPFC in encoding and expression of recognition memory during a social odor task. In the same animals, we also assessed the role of the mPFC in sustained attention using the rodent psychomotor vigilance test (rPVT). The social odor recognition task involves three phases (familiarization, habituation, and recognition) and requires olfactory-based discrimination between familiar odors and novel odors from conspecifics; failure to show preference for novel odors on the test phase indicates a memory deficit. The rPVT is a sustained attention test that measures accuracy, premature responding, and responses times to the presence of a stimulus light that appears after a random waiting period, between 3-10 seconds. pAAV-hSyn-hM4D(Gi)-mCherry was injected bilaterally into the mPFC and then prior to specific phases of behavioral testing, clozapine-N-oxide (CNO), was systemically injected to temporarily and remotely silence mPFC neurons. The results of the social recognition task revealed that CNO (1 mg/kg, i.p.) 30 min prior to the habituation phase was without effect on performance during habituation, but did impair memory for a novel odor the following day during the recognition test. These effects were not likely a function of CNO drug state because the impairment was observed during the drug-free test, which occurred 24-hrs after the CNO injection. In a second experiment designed to measure mPFC-mediated attention and performance, rPVT sessions were conducted after CNO administration (0 - 5 mg/kg, i.p., depending on session) and revealed that a dose of 1 mg/kg of CNO resulted in premature responding, but not impaired response times. These data show that silencing the mPFC impaired performance of recognition memory, without

inducing a motor impairment in the psychomotor vigilance test, indicating that the mPFC could be involved in the encoding and consolidation of information about social odors.

Disclosures: S. Robinson: None. **S.J. Aldrich:** None. **L. Granata:** None. **R.D. Heinz:** None. **C.M. Davis:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.09/FFF24

Topic: H.01. Animal Cognition and Behavior

Title: Alteration in the brain induced by memory retrieval

Authors: *M. MARUI[1], K. ADACHI[1], S. TOMONAGA[2], T. HAYASHI[1], M. NAGASAWA[1]
[1]Meijo Univ., Nagoya city/ Aichi prefecture, Japan; [2]Kyoto Univ., Kyoto city/ Kyoto prefecture, Japan

Abstract: Background: Dementia is a social issue to be solved. World Health Organization reported that 50 million people are suffering from dementia around the world, and the number of subjects will grow year by year. Memory impairment is one of characteristic symptoms of dementia and lead the reduction of ‘‘Quality Of Life’’. Therefore, the therapeutic treatment and prophylaxis of memory impairment needs to be established. Memory function is consisted of three processes, ‘’encoding’’, ‘’storage’’ and ‘’ retrieval’’, and many dementia patients impaired their retrieval processes. However, the retrieval mechanism in memory function remains unclear. Thus, the aim of the present study was to establish an animal model which is effective to elucidate the mechanism for retrieval process. In addition, the alterations that retrieval process induced in the brain were evaluated.
Material and Method: Object recognition test (ORT) with some modifications was performed to enhance a memory retrieval. Male 8-week-old ICR mice were allowed to explore in the black square arena with two identical objects for 5 min. This trial was performed once a day for 3 days. On 4th day, control (CON) mice explored the familiar objects for 3 min, while ‘‘memory retrieval’’ (MR) mice explored an identical object and a novel object. Mice tend to show an interest in a novel object. Accordingly, a ratio of latency to explore a novel object on 4th day, an index of retrieval-based behavior of MR mice was calculated form the following formula; 100 × latency exploring a novel object /latency exploring both objects. In CON mice, an expediential ratio of latency to explore a novel object was estimated by a similar method. After these trials, mice were sacrificed under anesthesia and their brains were immediately dissected several regions. Protein expression analysis in the hippocampus and cerebral cortex was verified by two-dimensional electrophoresis, and metabolites in the hippocampus were determined by GC-MS
Result: A ratio of latency to explore a novel object of MR mice was significantly higher than

those of CON mice (MR mice: 73.7±3.5%, CON mice: 52.5±2.6%). This result shows that MR mice recognized a familiar object. Consequently, it was suggested that an animal model established in the present study was useful for enhancing a memory retrieval. The protein expressions in the hippocampus and cerebral cortex were changed due to the retrieval process. Several novel protein spots expressed in MR mice comparing CON mice. Additionally, the concentrations of a metabolite and an amino acid in MR mice were significantly lower than those in CON mice. These metabolites may be possible to utilize as biomarkers for dementia.

Disclosures: M. Marui: None. **K. Adachi:** None. **S. Tomonaga:** None. **T. Hayashi:** None. **M. Nagasawa:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.10/GGG1

Topic: H.01. Animal Cognition and Behavior

Support: Commonwealth Universal Research Enhancement (CURE) Program to Yan-Chun Li
RO1MH085666 grant to W.J. Gao

Title: The role of Igsf9b in prefrontal cortical function

Authors: *C. ALEXANDROPOULOS, S. YANG, N. MACK, Y.-C. LI, W.-J. GAO
Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: The medial prefrontal cortex (mPFC) plays an important role in psychiatric illnesses. GWAS studies suggest that mutations in gene *IGSF9B* correlate with negative symptoms of schizophrenia and depression in humans. It is reported that Igsf9b, coded by *IGSF9B,* is widely distributed in neocortex and localized at inhibitory synapses. However, little is known about the function of Igsf9b in mPFC-dependent behaviors. To investigate this, we knocked down Igsf9b in the mPFC by bilaterally injecting AAV5-GFP-U6-mIGSF9b-shRNA into mPFC of male and female C57BL/6 mice. To assess behavioral phenotypes mimicking psychiatric illnesses, the following behavioral tasks were employed: locomotion, T-maze forced alternation, three chamber sociability, and forced swim tasks. Preliminary data indicated that Igsf9b knockdown in male mice took longer to reach criterion in the T-maze task, suggesting potential learning deficits. However, their performance in the working memory task did not differ from the scramble control male mice. Additionally, Ifsf9b knockdown males displayed a reduced social interaction in the three-chamber task compared to control males. Conversely, Igsf9b knockdown in female mice did not show distinct differences from control female mice in both T-maze and three-chamber tasks. However, female, but not male, Igsf9b knockdown mice exhibited increased hyperactivity in the locomotion task compared to control female mice. Both male and

female Igsf9b knockdown mice did not differ from control mice in the forced swim task, suggesting no sign of depressive behavior These results suggest that Igsf9b mutations may impact negative symptoms in schizophrenia, with sex differences, but it may not contribute to depressive symptomatology.

Disclosures: C. Alexandropoulos: None. **S. Yang:** None. **N. Mack:** None. **Y. Li:** None. **W. Gao:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.11/GGG2

Topic: H.01. Animal Cognition and Behavior

Support: Erasmus Mundus Expert Sustain II (2016-17)
Royal Society Commonwealth Travel Grant (2017-2018)

Title: Social dominance in a rat model of fragile-X syndrome

Authors: *K. SAXENA[1], J. WEBSTER[1], A. HALLAS-POTTS[1], R. MACKENZEI[2], G. TAYLOR[1], P. SPOONER[1], D. THOMSON[1], P. KIND[1,3,4,5], S. CHATTARJI[6,3], R. MORRIS[1,3,4,5]
[1]Univ. Of Edinburgh, Edinburgh, United Kingdom; [2]Univ. of Cambridge, Cambridge, United Kingdom; [3]Ctr. for Brain Develop. and Repair, Bangalore, India; [4]The Patrick Wild Ctr., Edinburgh, United Kingdom; [5]Ctr. for Discovery Brain Sci., The Univ. of Edinburgh, Edinburgh, United Kingdom; [6]Natl. Ctr. for Biol. Sci., Bangalore, India

Abstract: The neurodevelopmental disorder, Fragile-X, is the most common inherited, monogenetic cause of intellectual disability. It is caused by the mutation in the Fmr1 gene resulting in a decrease in the production of fragile- x mental retardation protein (FMRP). One of the primary symptoms of a child suffering with Fragile-X is difficulty in social interaction. Modeling the syndrome in rodents has revealed cns abnormalities (anatomical and physiological) that could lead to better understanding, but there has so far been little study of social interactions in relation to this condition (c.f. de Esch et-al.*Neurobiolol.Dis.*2014). Subjects: We have used a Fmr1 Knock-out rat model and examined the impact on social dominance and hierarchy using tube-test (Wang et-al.*Science.*2011). The study was performed on 56 rats, housed 4 animals/cage, with cages of KOs (Fmr1 Knock-outs, n=4) or WTs (Wild types, n=3) or Mixed lines (2 KO and 2 WT, n=7). Results: *Phase 1:* The hierarchy was measured 10 sessions of pairwise interactions between all animals of a cage using the tube-test. A social hierarchy was shown by both KOs and WTs, with the hierarchy in WT cages being significantly less variable ($t=2.99$, $df=26$, $p=0.006$) relative to KO cages. In this variability, it appeared that KOs displayed a bimodal distribution whereby some animals were "hyper stable" and others "hyper-unstable".

In mixed cages, WT animals were relatively more dominant over the KOs (Chi-square=14.63, df 1, p=0.0001). *Phase 2*: Animals in different cages were then also tested in a pairwise manner. The WT dominance phenotype was lost in stranger encounters, with prior experience having a larger effect, i.e animals that were high ranking in the phase 1 tended in phase 2 also (Chi-square=102, df=1, p<0.0001). However, paradoxically, KO won more contests than WTs when higher rankers competed, but the pattern was reversed for low-ranking contests. This intriguing finding could possibly be explained by the cognitive inflexibility or repetitive behaviour phenotype that is observed in Fragile-x animals, arguably analogous to what is seen in humans. Detailed behaviour profiling (pushing, resistance, withdraw etc.) revealed that high-ranked animals showed significantly more pushes (F (5,84)=12.5, p<0.001) and less 'retreats' (F (5,84)=12.5, p<0.05) relative low ranked rats. Conclusion: Even though the fragile-x is a monogenic condition, experience has an impact on the stability of rank and upon interactions with other animals, possibly mediated by synaptic alterations on thalamic prefrontal pathways (Zhou et-al.*Science*.2017). Nature and nurture are important and should be considered in the development of therapeutics.

Disclosures: K. Saxena: None. **J. Webster:** None. **A. Hallas-Potts:** None. **R. Mackenzei:** None. **G. Taylor:** None. **P. Spooner:** None. **D. Thomson:** None. **P. Kind:** None. **S. Chattarji:** None. **R. Morris:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.12/GGG3

Topic: H.01. Animal Cognition and Behavior

Support: PICT 20150-2344

Title: Analysis of the role of 5-HT2aR as a target for enhanced social cognition and episodic memory

Authors: *N. V. WEISSTAUB[1], A. SACSON[2], J. F. MORICI[2], P. BEKINSCHTEIN[3]
[1]Inst. de Neurociencia Cognitiva Y Traslacional, Buenos Aires, Argentina; [2]Inst. de Neurociencia Cognitiva y Traslacional, Ciudad Autonoma de Buenos Aires, Argentina; [3]Inst. de Neurociencia Cognitiva y Traslacional, Ciudad Autonoma Buenos Aires, Argentina

Abstract: Social Cognition encloses a large variety of behaviors and it is a domain commonly affected in psychiatric disorders. Serotonin has been linked to social behavior in humans due to its association with the regulation of mood and anxiety behaviors and also due to the use of selective serotonin reuptake inhibitors as the first line of treatment for a large number of these disorders. Recently it has become clearer that episodic memory systems can interact with social

cognitive processes and that appropriate memory processing is important to navigate the social world. Interestingly, somebrain areas involved in social cognition overlap with the ones involved in episodic memory. In this work we analyzed if chronic administration of the antidepressant fluoxetine (FLX) affects social interaction and memory processes and a putative role of 5-HT2aR in this effect. For this purpose, we administrated a chronic oral dose of FLX (10 mg/kg) to wild type (WT) and 5-HT2aR knockout mice (KO). After 4 weeks of FLX administration, the animals performed a series of behavioral tasks that include novelty suppressed feeding (NSF), social interaction (SI) and novel object recognition (NOR). We used a NOR task with a 3 min training session that was not enough to generate a long-term NOR memory at 24 h in WT or KO mice. Interestingly, after FLX treatment WT but not KO mice remembered having seen the familiar object during a test performed 24 h after training. We observed no interaction between genotype and treatment when mice were trained to generate a long.term memory. In the social interaction task, chronic FLX increased the exploration time of the social stimuli in WT but not in KO mice. These results suggest that chronic fluoxetine can influence social interaction and episodic like memory and that these effects are at least partially mediated by 5-HT2aR.

Disclosures: N.V. Weisstaub: None. **A. Sacson:** None. **J.F. Morici:** None. **P. Bekinschtein:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.13/GGG4

Topic: H.01. Animal Cognition and Behavior

Support: Human Frontier Science Program
Children Tumor Foundation

Title: mTOR-dependent interferon signaling in microglia and social memory deficits in a mouse model of tuberous sclerosis

Authors: *M. F. LOPEZ-ARANDA[1,2,3], I. CHATTOPADHYAY[6], G. M. BOXX[4], E. R. FRALEY[5], T. SILVA[1,2,3], M. ZHOU[1,2,3], M. PHAN[1,2,3], R. MANDANAS[1,2,3], K. BACH[1,2,3], S. LIU[8], N. LI[8], G. CHENG[4], A. RZHETSKY[7], S. A. WHITE[5], Y. ZHOU[8,9], A. J. SILVA[1,2,3]
[1]Neurobio., [2]Integrative Ctr. for Learning and Memory, [3]Brain Res. Inst., [4]Microbiology, Immunol. & Mol. Genet., [5]Integrative Biol. & Physiol., Univ. of California Los Angeles, Los Angeles, CA; [6]Med., [7]Human Genet., Univ. of Chicago, Chicago, IL; [8]Dept. of Physiol. and Pathophysiology,, Sch. of Basic Med. Sci., Shandong, China; [9]Inst. of Brain Function and Dis. Qingdao Univ., Shandong, China

Abstract: There is growing evidence that environmental factors, such as immune activation, contribute to the severity and range of cognitive phenotypes in neuropsychiatric disorders. However, the cell types and the molecular mechanism(s) responsible for these cognitive phenotypes remain unclear. We have multiple lines of evidence that in male mice with a tuberous sclerosis mutation ($Tsc2^{+/-}$), immune activation during a critical phase of post-natal development, triggers an mTOR-dependent, self-perpetuating cycle of IFN production in microglia. This disrupts hippocampal plasticity and causes behavioral phenotypes, including social memory deficits as well as alterations in ultrasonic vocalization patterns (USV), under conditions that do not affect either wild type or female mice. Importantly, our human epidemiological studies show a strong correlation between the prevalence of infections during childhood, and a future diagnose of neuropsychiatric disorders, suggesting that our results in mice are mirrored by human findings. These results open new therapeutical opportunities for neuropsychiatric disorders, and demonstrate the critical importance of microglia during early post-natal development in cognitive function, including social memory.

Disclosures: M.F. Lopez-Aranda: None. **I. Chattopadhyay:** None. **G.M. Boxx:** None. **E.R. Fraley:** None. **T. Silva:** None. **M. Zhou:** None. **M. Phan:** None. **R. Mandanas:** None. **K. Bach:** None. **S. Liu:** None. **N. Li:** None. **G. Cheng:** None. **A. Rzhetsky:** None. **S.A. White:** None. **Y. Zhou:** None. **A.J. Silva:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.14/GGG5

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI / 16K00380 to R.K., 17H00740, 17H06031 to Y.K

Title: Contribution of nucleus accumbens to impulsive choice behavior based on the last reward experience

Authors: *J. YUZA[1], M. OKUBO[2], Y. KOMURA[3], R. KAJIWARA[4]
[1]Meiji Univ., Kanagawa, Japan; [2]Meiji Univ., Kawasaki, Japan; [3]AIST, Tsukuba, Japan; [4]Meiji Univ. / Dept. of Electro. & Bioinfo., Kawasaki, Japan

Abstract: The nucleus accumbens (NAc) is proposed to be critical in integrating various kinds of information to control impulsive behavior (Basar et al. 2010). Actually, previous anatomical studies suggest that the NAc is a part of larger neural network including the limbic structures as well as motor structures, by which the NAc could integrate the value of expected rewards with the impulsive-motor planning. In the present study, we designed the two-choice task using modified M-shaped-maze for investigating the waiting behavior for delayed reward in rats, and

investigated the involvement of the NAc. In the center lane of M-shaped-maze, we mounted an infrared sensor, which cue-triggered the start of reinforcement tone stimulus (8kHz, 70dB) from the right or left lane. The stimulus was presented at the correct lane where rat obtained the sucrose reward. There is a "waiting-zone" at the exit of center lane, just in the middle of a path connecting the right and left lanes. At the waiting-zone, a light emitting diode (LED) was mounted to signify the end of waiting period to rats. And the rat has to wait at waiting-zone before going into the correct lane until the LED switched on, subsequently the solenoid valve connected to the drinking port was opened. The experimental system was controlled by original software developed on the LabVIEW platform, and the waiting period, i.e. "*delay* for the reward" was presented randomly (0, 5, 10, 15 20, 25 seconds). In the test sessions of the behavioral task, the probability for rats to obtain the rewards is more than 50% when the delay was shorter than 15 sec. Concerning to the numbers of unrewarded trials, both "waiting-error" and "choice-error" were observed. As the delay increased, the waiting-error increased, but the choice-error was not increased. In addition, waiting error seemed to be correlated with the delay period presented in the previous trial. This observation indicates that our behavioral paradigm might measure the mnemonic function as well as the control of impulsion. Inactivation of the NAc by injecting the fluorescent muscimol which is an agonist of gamma-aminobutyric acid-A receptor revealed that the NAc would be critical for waiting behavior but not for the mnemonic trace produced in a previous trial.

Disclosures: J. Yuza: None. **M. Okubo:** None. **Y. Komura:** None. **R. Kajiwara:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.15/GGG6

Topic: H.01. Animal Cognition and Behavior

Title: Striatal electrophysiological fingerprint during social interaction in freely moving rats

Authors: *R. L. REDONDO[1], R. LUETOLF[1], J. TAMPE[1], O. FAJARDO[2], M. BAINIER[1], P. SCHOENENBERGER[1]
[1]pRED, NORD, [2]pREDi, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Abstract: The ventral striatum (VS) is a key node in the brain circuitry controlling motivation, decision making, sociability, and reward processing. Excitatory input from cortical and limbic structures, as well as prominent dopaminergic signals, converge in the VS. While in humans, diminished fMRI BOLD striatal responses to social reward have been reported in Autism (Scott-Van Zeeland et al. 2010), in rodents, gamma oscillations (GO) in the striatum have been linked to reward expectation and delivery (van der Meer et al. 2010). In relation to sociability, increases in GO in the prefrontal cortex have been linked to social cues in mice (Cho et al. 2015).

The goal of this study was to investigate striatal electrophysiological responses to social cues in freely moving rats. Sprague-Dawley rats with single wire electrodes in the VS explored an open field arena with two Plexiglas boxes inserted in opposite corners. The boxes had rows of small holes in order to facilitate visual, audible and olfactory exploration. The main sociability experiment consisted of two blocks with three contiguous sessions each: The first session being 10 min with empty Plexiglas boxes; the second session being 15 min with an unfamiliar conspecific in one insert and an object in the other; and the third session being 5 min with empty boxes again. After this first block, pharmacological compounds could be administered; Vehicle was used for the assay development described here. 30 min after compound administration the second block was repeated with the same specifications. Video-tracking allowed us to segment brain activity, according to the position of the nose of the experimental animal (object (OZ), animal (AZ) and neutral zone (NZ)).
Our data show an increase in the power of GO specific to i) within a session, when in the AZ versus NZ and OZ; ii) between sessions, when the AZ contains a conspecific compared to the same zone when empty.
In summary, the VS shows higher 80 Hz GO power in proximity to social cues compared to inanimate objects or empty environments. There was a dissociation between behavior and electrophysiology in that the degree of increase in GO did not correlate with the behavioral prosocial response. We are searching for manipulations that specifically affect the VS responses to social cues.

Disclosures: R.L. Redondo: None. **R. Luetolf:** None. **J. Tampe:** None. **O. Fajardo:** None. **M. Bainier:** None. **P. Schoenenberger:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.16/GGG7

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant UL1TR001108
NIH Grant R01MH106568
Indiana Spinal Cord and Traumatic Brain Injury Research Fund #19920

Title: Role of orbitofrontal cortex in social recognition and social-enhanced safety learning in rats

Authors: *K. D. ANDREWS[1,2,3], E. A. LUNGWITZ[1,3], A. D. DIETRICH[1,4], N. S. RACE[2,6], S. MAJUMDAR[1,3], R. SHI[6,7], T. W. MCALLISTER[1,5], W. A. TRUITT[1,4]
[1]Stark Neurosciences Res. Inst., [2]Med. Scientist Training Program, [3]Program in Med. Neurosci.,

[4]Anat. and Cell Biol., [5]Psychiatry, Indiana Univ. Sch. of Med., Indianapolis, IN; [6]Weldon Sch. of Biomed. Engin., [7]Basic Med. Sciences, Col. of Vet. Med., Purdue Univ., West Lafayette, IN

Abstract: Social processes are pervasive to daily human culture and critical for mental wellbeing. Social cues, such as the presence of a familiar social partner, can serve as signals to help discriminate environmental stimuli as safe or fearful. This "Social-Enhanced Safety Learning" is critical for preventing chronic fear and anxiety. Social-Enhanced Safety Learning is modeled in rats, which learn to reduce anxiety-like response to an anxiogenic stimulus via recurring presence of a social partner during the anxiogenic exposure; this paradigm is termed Social Familiarity-induced Anxiolysis (SoFiA). Rats exposed to traumatic brain injury (TBI) fail to acquire SoFiA. TBI rats demonstrate accumulated neurotoxin and altered excitatory/inhibitory signaling in orbitofrontal cortex (OFC), a region that may contribute to TBI-induced SoFiA deficit due to its known regulation of social, emotional, and cognitive behaviors. To investigate this, gene expression of GABA and Glutamate-related genes were compared between TBI and sham rat OFC. OFC of TBI rats had higher expression of metabotropic glutamate receptor types 1 and 5 (mGluR1/5) compared to OFC of sham rats. Non-injured rats injected with selective mGluR1/5 agonist, but not saline vehicle, into OFC failed to acquire SoFiA behavior, suggesting OFC may play a key role in acquiring SoFiA. To investigate this, rat OFC was temporarily inhibited with $GABA_A$ agonist, Muscimol, daily prior to SoFiA behavior training sessions. Rats receiving Muscimol injections failed to acquire SoFiA unlike their saline-vehicle injected counterparts. SoFiA is a complex behavior requiring social, emotional, and cognitive processes. To begin delineating which component(s) of SoFiA the OFC may be regulating, rats with either intact or inhibited (via Muscimol) OFC were assessed for social preference and social recognition behaviors. While social preference was unaffected by OFC inhibition, social recognition was impaired. In addition, injection of mGluR1/5 agonist into OFC impaired social recognition. These converging lines of evidence suggest that OFC plays a key role in social recognition and disruption of OFC-mediated social recognition processes may impair more complex behaviors such as Social-Enhanced Safety Learning.

Disclosures: K.D. Andrews: None. **E.A. Lungwitz:** None. **A.D. Dietrich:** None. **N.S. Race:** None. **S. Majumdar:** None. **R. Shi:** None. **T.W. McAllister:** None. **W.A. Truitt:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.17/GGG8

Topic: H.01. Animal Cognition and Behavior

Support: JSPS KAKENHI Grant JP15K04180
JSPS KAKENHI Grant JP16K04419

Title: Social enrichment enhances, while social isolation impairs, social recognition memory in male rats

Authors: *M. TOYOSHIMA, M. SUGITA, Y. ICHITANI, K. YAMADA
Univ. of Tsukuba, Tsukuba-Shi, Japan

Abstract: Memory span, which means the maximum number of items to be memorized at once, is an index for evaluating the animals' memory ability as well as the length of retention period of memory. We previously reported that the housing environment during the developmental period affected social, but not object, memory span in adult rats. The rats housed with many cage mates (social enrichment) were able to memorize more conspecifics at once compared to the rats housed singly (social isolation). In the present study, we compared social memory span between social isolated and social enriched rats in terms of a longer retention period. Wistar-Imamichi male rats were assigned to one of two groups at 21days age: social isolation or enrichment. In the social isolation group, the subjects were housed singly in standard cages, while socially enriched rats were housed in groups of ten in a large cage. Social memory test was started at 10 weeks old. In the sample phases, the subject rats were allowed to freely explore an open-field arena in which 2 or 5 different juveniles were presented for 5 min. The sample phases were repeated 3 times with 5 min ITI. Fifty min after the third sample phase, subjects were again placed in the field in which one of the sample juveniles was replaced with a novel juvenile, and their exploration behavior to each juvenile was analyzed. Socially enriched rats were able to discriminate a novel conspecific from the other familiar ones in both of 2- and 5-item conditions, while socially isolated rats failed to discriminate between novel and familiar conspecifics even under the 2-item condition. These results suggest that social enrichment enhances rats' social memory ability including memory span and retention period, whereas social isolation impairs the ability.

Disclosures: M. Toyoshima: None. **M. Sugita:** None. **Y. Ichitani:** None. **K. Yamada:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.18/GGG9

Topic: H.01. Animal Cognition and Behavior

Support: JSPS KAKENHI 16H01490
JSPS KAKENHI 18K07357

Title: Activation of oxytocin receptor-expressing neurons in anterior cingulate cortex during helping behaivor in rats

Authors: *A. YAMAGISHI, N. SATO
Dept. of Psychological Sci., Kwansei Gakuin Univ., Nishinomiya, Japan

Abstract: The neuropeptide oxytocin may affect social behavior, and it is known that the oxytocin receptors are expressed in anterior cingulate cortex, insular, and amygdala. In this study, we examined c-fos expression of the oxytocin receptor-expressing neurons in these regions when rats show helping behavior. An experimental box consisted of pool and ground areas, and the pool area had water with the depth of 40 mm. The two areas were partitioned by a clear plate with a hole which connects the two areas. A clear circular door closed the hole. The rats were housed in pairs for 14 days. After the housing period, one of the pair was assigned to a helper. The helper was placed in the ground area, and his cagemate was locked in the pool area. When the helper opens the circular door, the cagemate can escape from the pool area. We behaviorally tested whether the helper opens the door to help the cagemate for 10 days. The helper rats were divided into Early, Late and Control groups. The Early group was tested until the helper shows the door-opening behavior 2 times. The Late group was tested until the helper shows that consecutive 3 times in 90 sec. The Control group were never tested. We compared the number of c-fos positive cells of oxytocin receptor-expressing and not expressing neurons in anterior cingulate cortex, insula, and amygdala of the 3 groups using triple immunofluorescent labeling. As a result, in the anterior cingulate cortex, there were more c-fos positive neurons in the Late group than that of the Control group regardless of the oxytocin receptor expression. This result suggests that neural activity of anterior cingulate cortex may play a role in helping behavior.

Disclosures: A. Yamagishi: None. **N. Sato:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.19/GGG10

Topic: H.01. Animal Cognition and Behavior

Title: Rousseau's rats. Cooperation, communication and constructing social contracts in an iterated Stag Hunt task

Authors: *S. M. RENNIE, E. J. DEWITT, A. SILVA, J. FRAZAO, M. MOITA
Fundação Champalimaud, Lisboa, Portugal

Abstract: Coordinating cooperative behaviors, the basis of social contracts, is fundamental for animals to form complex societies. To model coordinated behavior in rodents, we developed a task that tests rats in a risky Stag Hunt (SH) game. In the SH players choose either to risk cooperating for a high reward, which is risky, as it requires a coordinated cooperative choice or

to defect and receive a moderate safe reward regardless of the other's choice. The SH has two pure equilibrium strategies, mutual cooperation, which maximizes reward, and mutual defection, which minimizes risk. A third equilibrium is a mixed strategy (MS) where both rats independently cooperate with a probability that renders the utility of cooperating the same as that of defecting, minimizing risk. However, if rats coordinate their cooperative choices they can also increase their gains.In our task each rat could observe the other during decision making. Social information and reward contingencies could be precisely controlled whilst body and head position were tracked. This allowed us to ask whether, and under what conditions, freely behaving rat dyads were capable of coordinated cooperation and which, if any, equilibria behavior would be adopted. We tested 10 rat dyads and found that they overcame an initial preference for defection establishing high levels of stable cooperation close to the MS equilibria. Dyads rapidly re-established this behavior following a reversal of the assignment of cooperate and defect arms, demonstrating that rats made choices flexibly and had a strong preference for the MS strategy. Manipulating social information revealed that rats use social cues for generating and stabilizing strategic coordinated cooperation that relied on learning the contingencies between the behavior of others and outcomes. Using GLMs we show that rats built a model of the other's choices based on recent trial history. However, the rats' trajectories reflected changes-of-mind that occurred more often on trials were behavior contradicted model predictions, indicating rats revised their choice based on the other rats' behavior. Including the other's choice in the current trial improved the model's predictive accuracy. Over sessions rats were less variable and showed fewer changes-of-mind. More direct trajectories constitute clearer cues that could be used to improve coordination. Rats can solve the cooperation problem selecting a MS equilibrium, in a risky SH task to establish a rudimentary social contract. They do this by refining and interpreting social cues and building models of their opponents' choices, showing a level of socio-eonomic sophistication rarely seen outside of primate lineages.

Disclosures: E.J. Dewitt: None. **A. Silva:** None. **J. Frazao:** None. **M. Moita:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.20/GGG11

Topic: H.01. Animal Cognition and Behavior

Support: IBS-R001-D1

Title: Searching for neural substrate underlying rule-observance behavior of competing mice in social conflict

Authors: *J. BYUN, A. ALKAHWAJI, H.-S. SHIN
Ctr. for Cognition and Sociality, Inst. For Basic Sci., Daejeon, Korea, Republic of

Abstract: Violating social rules might bring immediate individualistic profit, whereas orderly resolution by consent rules requires patience, but enhances long-term mutual benefit. However, the neural circuits mediating these socio-economical strategies are remained unclear. Here, we developed modified two-armed maze that uses wireless electrical brain stimulation as reward. First, the mice were individually operant-trained to initiate and then receive the reward at the signaled arm. Then, two mice were coupled and had to cooperate to initiate reward but then to compete over reward allocation. Mice develop and observe a rule of reward zone allocation that increases the total amount of reward and reward equity between the pair. Now we are investigating on the role of medial prefrontal cortex (mPFC) in reward zone allocation by using chemogenetic DREADD system and in vivo unit recordings. These results will provide a framework for understanding the circuit basis of interactive social behavior.

Disclosures: J. Byun: None. **A. Alkahwaji:** None. **H. Shin:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.21/GGG12

Topic: H.01. Animal Cognition and Behavior

Support: LISBOA-01-0145-FEDER-007391
FCT PTDC/DTP-FTO/3346/2014
FCT SFRH/BD/89582/2012

Title: Age affects social interaction and social novelty seeking in mice

Authors: *A. C. BARCELOS[1,2,3], F. MOURO[1,2], A. SEBASTIÃO[1,2]
[1]Faculdade de Medicina da Univ. de Lisboa, Inst. De Medicina Mol., Lisbon, Portugal; [2]Inst. de Farmacologia e Neurociências, Faculdade de Medicina, Univ. de Lisboa, Portugal, Lisbon, Portugal; [3]Serviço de Psiquiatria, Hosp. Garcia de Orta, Almada, Portugal

Abstract: Sociability in later life and its importance for heathy ageing has been gathering interest in recent years. The positive emotions that are related and experienced during social interactions represent the central reason behind the benefits of social interaction on cognitive processes. In fact, elder people less satisfied with their social networks show greater reductions in cognitive functioning over time. Furthermore, neurodegenerative diseases can be associated with social withdrawal and modifications in social behavior in elder people. How age itself affects social behavior without major interference with other life style confounding variables is difficult to disentangle in human studies. In this work we used the mouse as mice as animal model, to assess how sociability is affected by age. Sociability and reaction to social novelty was evaluated through the Three-Chamber Sociability and Social Novelty Test. On a first stage, to

test sociability, animals had the opportunity of interacting with an unknown conspecific of the same age and gender or with an inanimate object. On a second stage, to study social novelty seeking behaviour, animals were presented with a social novelty, by replacing the object with a new unknown conspecific. Anxiety and locomotion scores were assessed on the Open-Field Test (OFT). Control adult animals (15 weeks old), showed a preference for interacting with an unknown conspecific and also a marked preference towards social novelty, spending more time interacting with a novel partner than with a familiar one. Interestingly, old mice (60 weeks old) did not display the tendency for interacting with the conspecific observed in adult animals. Besides sociability, the social novelty preference of these animals was also affected. Importantly, there were no significant differences on the Open Field Test (OFT), when evaluating motor abilities and anxiety for adult and old animals. Also, by comparing the percentage of time spent interacting with the different stimuli (conspecific, object or social novelty), there were no marked reductions on the exploratory drive of old animals when comparing with adult ones. This data allow excluding deficits in locomotion, reduction in the motivation to explore, and also, anxiety increases, as contributors for the observed results. Being so, our data strongly suggests that age can play an important role in sociability since old animals displayed decreases in sociability and social novelty seeking. These results highlight the impact of age on important social behaviors, thus pointing towards the need of active strategies designed minimize this naturally occurring tendency.

Disclosures: A.C. Barcelos: None. **F. Mouro:** None. **A. Sebastião:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.22/GGG13

Topic: H.01. Animal Cognition and Behavior

Support: NSERC Grant 400212 (EC)
NSERC Canada Graduate Scholarship (KE)
University of Guelph President's Scholarship (PS)

Title: Muscarinic acetylcholine receptors play a role in social learning in female mice

Authors: *K. S. ERVIN[1], S. HOWARD[1], P. SANKAR[1], E. CHOLERIS[2]
[2]Psychology, [1]Univ. of Guelph, Guelph, ON, Canada

Abstract: Social learning is a unique form of cognition in which an animal acquires information from a conspecific, rather than individually through trial and error. Social learning is common and important in many animals and in humans, but we know little about the underlying neurobiological mechanisms. Social learning can be studied using the social transmission of food

preferences (STFP), a natural learning phenomenon in rodents. In the STFP, an observer prefers a food it smelled on the breath of a conspecific demonstrator over other novel food choices. From studies using the general muscarinic acetylcholine receptors (mAChR) antagonist scopolamine, we know that mAChRs are involved in acquisition of a socially learned food preference (Boix-Trelis et al, 2007, Neurobiol Learn Mem, 87:659; Carballo-Márquez et al, 2009, Hippocampus, 19:446; Carballo-Márquez et al, 2009, Neurobiol Learn Mem, 91:98). However, we still do not know which specific mAChR subtypes drive these effects on social learning. The M1 and M2 receptor subtypes are involved in other types of learning and therefore could also play a role in the STFP (Van Der Zee and Luiten (1999). Prog Neurobiol, 58:409). Our aim was to determine whether M1 or M2 blockade with dicyclomine or AFDX-116, respectively, would disrupt social learning in the STFP. Female CD1 observer mice were treated intraperitoneally with dicyclomine (1, 4, 8, 16, or 32mg/kg) or AFDX-116 (1, 3, 6, or 12mg/kg) 30min prior to a social interaction with a demonstrator. Observers were then individually housed and tested for food preference 48h later. Social learning was blocked by the highest dose of dicyclomine (32mg/kg), suggesting that M1 mAChRs may play a role in social learning. Since the effect occurred only at the highest dose, there may have been a loss of selectivity and other subtypes may be involved. Results of the STFP with the M2 antagonist AFDX-116 will futher elucidate the respective roles of the M1 and M2 receptors. Our findings help to clarify how the cholinergic system mediates social learning, an important yet understudied form of learning in humans and animals.

Disclosures: K.S. Ervin: None. **S. Howard:** None. **P. Sankar:** None. **E. Choleris:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.23/GGG14

Topic: H.01. Animal Cognition and Behavior

Support: DC 04845
Schmitt Program for Integrative Neuroscience

Title: Memory and integration of faces and vocalizations in neuronal populations in the primate prefrontal cortex

Authors: *S. SHAH[1], T. LINCOLN[2], K. KEVELSON[2], L. M. ROMANSKI[2]
[1]Neurosci., Univ. of Rochester Sch. of Med. and Den, Rochester, NY; [2]Dept Neurosci., Univ. of Rochester Sch. of Med. and Dent., Rochester, NY

Abstract: The ventrolateral prefrontal cortex (VLPFC) plays an important role in language and communication. Previous studies have shown that VLPFC neurons respond to and integrate face

and vocalization stimuli and hold information about these stimuli online during working memory. Prefrontal neurons are highly selective in their responses to specific auditory and visual stimuli. Moreover, the magnitude and direction of multisensory responses is dependent upon particular combinations of faces and vocalizations, as well as their temporal synchrony and semantic congruence. Furthermore, neighbouring cells show responses to similar modalities and categories of stimuli. This suggests that there may be a topographic organization of the features encoded and integrated by single prefrontal neurons. However, real-world approximations of brain function require that we investigate memory and perception at the level of cell ensembles. Thus, in the current study, we used multiple single electrodes and linear electrode arrays to record simultaneously from multiple neurons while nonhuman primates performed an audiovisual working memory task using dynamic face and vocalization stimuli as the memoranda. Responsive neurons were further tested with additional exemplars of faces, vocalizations and their combination. We manipulated the stimuli along relevant feature axes including identity, vocalization category, semantic congruence, and temporal synchrony to investigate the salience of these features. We recorded from pairs and clusters of prefrontal neurons and assessed stimulus selectivity, task parameter selectivity and functional interactions between neurons within and across ensembles. By investigating the multisensory response structure at the level of neuronal ensembles in this manner, we will be able to determine what aspects of communication stimuli are being encoded and integrated by prefrontal neurons.

Disclosures: S. Shah: None. **T. Lincoln:** None. **K. Kevelson:** None. **L.M. Romanski:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.24/GGG15

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R03MH104851

Title: Contrasting characteristic behaviors in common laboratory mouse strain

Authors: R. SULTANA[1], *O. M. OGUNDELE[2], C. C. LEE[3]
[1]Comparative Biomed. Sci., [2]Louisiana State Univ., Baton Rouge, LA; [3]Comparative Biomed. Sci., Louisiana State Univ. Sch. of Vet. Med., Baton Rouge, LA

Abstract: Mice models are widely used to study various neurological disorders. From development to degenerative pathophysiology, the use of mice models has allowed for the study of disease mechanism and identification of therapeutic targets. Although the behavioral characteristics of these mice models are commonly used as assays for presumed neural alterations, the genetic background of these animals can strongly influence their baseline

behavior. Among the many mouse lines, the C57BL/6J, BALB/c, CBA and 129S inbred lines along with CD1 (an outbred line) are among the most commonly used to study neurological disorders, and associated pathology in the brain. However, comparing across studies that utilize different strains is complicated owing to an incomplete knowledge of between strain variability on commonly used behavioral metrics. Thus, in the present study we aimed to classify these strains behaviorally through several of the most commonly used behavioral tests: social interaction test, forced swim test, boli count, tail suspension test, stress calls, Y-maze, spontaneous alternation, pre-pulse inhibition. In our study we found that the animals behaved differently in terms of sociability/novelty, learning-memory, cognition, negative behaviors such as despair, stress calls etc. These results further bolster the effect of background genetics on behavioral phenotype as well as predisposition to neurological diseases. The latter also provides insight in to how genetics as a component must play a role in the susceptibility of some to the development of particular neurological diseases.

Disclosures: R. Sultana: None. **O.M. Ogundele:** None. **C.C. Lee:** None.

Poster

690. Animal Cognition and Behavior: Social Memory and Cognition I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 690.25/GGG16

Topic: H.01. Animal Cognition and Behavior

Title: Functional assessment of the neuronal circuits underlying social hierarchy through whole-brain IEG screening and targeted DREADD manipulation

Authors: *H. K. OYIBO, G. B. KELLER
Neurosci., Friedrich Miescher Inst. for Biomed. Resear, Basel, Switzerland

Abstract: Rank in a social hierarchy can determine access to shelter, food, mates and/or reproductive success; with dominant individuals receiving superior access to each at the detriment of subordinates. Social stratification offers benefits to subordinates as well, although they have restricted access to resources, a predefined pecking order minimizes risky conflicts with stronger dominate individuals reducing resources expended on clashes and unnecessary injuries. Perhaps for these reasons, in many animals, including humans, social hierarchy is determined early in a given social context and is fairly stable. However, it is still unclear what neural circuits underlie the formation, maintenance and flexibility of this interactive behavior. In order to interrogate the neural circuit mechanism of social hierarchy we have used fluorophore-linked immediate early gene (IEG) transgenic mice in social hierarchy ranking assays and screened brain-wide for regions differentially activated in low vs. high raking mice. We identified several such regions including orbital frontal cortex (OFC), and medial prefrontal cortex (mPFC). To determine the functional role of these regions in social behavior, we used

targeted DREADD (designer receptors exclusively activated by designer drugs) expression and manipulation. This provided us with evidence for the direct involvement of OFC in hierarchy behavior. Further experimentation will include the interrogation of the role of various cell types within in OFC in hierarchy behavior.

Disclosures: H.K. Oyibo: None. **G.B. Keller:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.01/GGG17

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01 MH110750

Title: Causal manipulations of live social gaze by microstimulating the primate prefrontal cortex

Authors: *S. FAN, O. DAL MONTE, N. A. FAGAN, C. C. J. CHU, S. W. CHANG
Psychology, Yale Univ., New Haven, CT

Abstract: A typical gaze interaction among two or more individuals is made up of a series of contingent behaviors that unfold over time. Correlative evidence from electrophysiological recording studies in non-human primates as well as neuroimaging studies in humans have shown that several regions in the prefrontal cortex, the superior temporal sulcus, as well as the basolateral amygdala (BLA) are implicated in social gaze processing. Our recent data support that different prefrontal areas as well as BLA encode various aspects of social gaze, and that prefrontal areas and BLA are synchronized during specific social gaze events (see Dal Monte et al., 2018 SfN abstract). However, the causal contributions of these brain regions in social gaze remain unknown. Here, we therefore tested whether and how causally manipulating specific populations of neurons impacts social gaze using a live gaze interaction paradigm, in which we can accurately record spontaneous social gaze behaviors between pairs of rhesus macaques. We investigated this question in three prefrontal areas—the anterior cingulate gyrus (ACCg), dorsomedial prefrontal cortex (dmPFC), and orbitofrontal cortex (OFC)—as well as BLA. We applied closed-loop microstimulations that are contingent upon specific social gaze events. Specifically, we triggered the onset of microstimulations by three distinct types of social gaze events—1) looking at the partner's face, 2) looking at the partner's eyes, and 3) mutual eye contact. We also explored some aspects of the microstimulation parameter space to characterize a set of parameters that can effectively and reliably modulate social gaze behaviors. Depending on the stimulated brain region and the type of gaze events triggering the microstimulation, we observed distinctive changes in social gaze behaviors. Our findings inform some of the causal workings underlying dynamic and contingent social gaze in the primate brain.

Disclosures: S. Fan: None. **O. Dal Monte:** None. **N.A. Fagan:** None. **C.C.J. Chu:** None. **S.W. Chang:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.02/GGG18

Topic: H.01. Animal Cognition and Behavior

Support: the Strategic Research Program for Brain Sciences from Japan Agency for Medical Research and Development, AMED

Title: Social action monitoring in the mirror and the mentalizing systems of the macaque brain

Authors: *T. NINOMIYA, A. NORITAKE, M. ISODA
Div. of Behavioral Develop., Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: Understanding others' actions and their consequences is of crucial importance for social life. Recent studies have revealed that the primate brain is equipped with two systems for processing such social information; the mirror system and the mentalizing system. However, it is still under debate as to how, if any, the two systems interact during social information processing. To address this issue, we trained monkeys to perform a role-reversal choice task. This is a turn-taking task involving two monkeys and required them to utilize each other's action for optimizing their own behavior. In each trial, one monkey was assigned as the actor and the other monkey as the observer. The roles of the actor and the observer alternated every three trials. The actor chose one of three targets while the observer holding his start button throughout the trial. Only one button was associated with a reward in each trial, whose position remained the same for a block of 11-17 trials. The position-reward contingency was changed in an unpredictable manner. Both monkeys were rewarded with a drop of water when the actor made a correct choice, whereas neither monkey was rewarded if the actor made a wrong choice. Neural activities were recorded simultaneously in the ventral premotor cortex (PMv) of the mirror system and the medial frontal cortex (MFC) of the mentalizing system using linear-array multicontact electrodes while the monkeys were performing the task. We found a set of neurons that were excited by the actions of its own, those of the partner, or both in each area. Some of these neurons differentiated the correct and error choices. The number of neurons selective for the partner's action in MFC was larger than that in PMv. The direction of information flow was investigated between PMv and MFC by applying a multivariate Granger causality analysis to local field potentials measured in each area. We found that Granger information flow was significantly larger from PMv to MFC than in the opposite direction during both action execution and action observation. These results indicate that PMv may provide MFC with information

related to others' ongoing action. We suggest that the mirror and mentalizing systems cooperate to predict others' action and its consequence.

Disclosures: T. Ninomiya: None. **A. Noritake:** None. **M. Isoda:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.03/GGG19

Topic: H.01. Animal Cognition and Behavior

Support: Alfred P Sloan Foundation

Title: Social curiosity in rhesus monkeys

Authors: *J. A. JOINER[1,2], N. A. FAGAN[1], S. W. C. CHANG[1]
[1]Psychology, [2]Yale Univ., New Haven, CT

Abstract: Learning about the world is a critical feature of cognition that allows animals to manipulate their environment. Animals derive value from many different sources, and these rewards can modify behavior. Primary reinforcers like food are rewarding, but animals also experience reward from other stimuli. Some of these sources of reward are intangible, like information. Like humans, monkeys find information inherently rewarding, displaying a preference to reveal information about upcoming primary reinforcers (Bromberg-Martin & Hikosaka, 2009).

Information has utility to an organism that can use it, such as knowing where food is. However, for animals living in social groups, acquiring information from or about others is necessary. This is especially true for nonhuman primates, which live in large and hierarchically organized societies, where processing social information can be just as critical to survival as information about food.

Here, we extend an information seeking paradigm designed by Bromberg-Martin and Hikosaka into the realm of abstract, social information. We first trained monkeys on an advance information seeking task, in which monkeys can choose to see a cue that tells them in advance how much juice they are about to receive in an environment with variable reward magnitude. The choice to receive that information does not alter the amount of juice received. We replicate their finding that monkeys prefer advance information about reward magnitude. Specifically, 75-95% of the time, monkeys chose advance information, with some individual differences.

We then trained monkeys on a social variant of this task. In the social information seeking, the animal can choose a cue that tells them in advance the facial expression of a picture of a monkey face that they will be viewing for 500ms, followed by a fixed reward amount that is always delivered upon the completion of each trial. Even though this cue does not impact which face the

monkeys will see, the monkeys prefer to know the valence of the face in advance 65-80% of the time. While preference is somewhat dampened in the social information seeking task, it is critical to note that this is an abstract level of information toward which animals can express curiosity. These results indicate that advance information seeking is not just an effect of curiosity toward a primary reinforcer, but also extends to curiosity about social information. Our results suggest that curiosity in nonhuman primates can be translated into increasingly abstract levels of information.

Bromberg-Martin, ES & Hikosaka O. Midbrain dopamine neurons signal preference for advance information about upcoming rewards. Neuron 63, 119-126 (2009).

Disclosures: J.A. Joiner: None. **N.A. Fagan:** None. **S.W.C. Chang:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.04/GGG20

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01 MH110750

Title: Neural coding of live social gaze interactions

Authors: *O. DAL MONTE[1], S. FAN[2], N. A. FAGAN[2], C. C. J. CHU[2], S. W. CHANG[2]
[1]Dept. of Psychology, [2]Yale Univ., New Haven, CT

Abstract: Gaze interaction, particularly eye contact, is central to social behavior. It allows individuals to communicate with one another and infer attention, emotion, and intentions from others. Single-neuron recording studies in non-human primates and neuroimaging studies in humans have indicated that several prefrontal cortical regions and the basolateral amygdala (BLA), among others, are implicated in the processing of social gaze. However, the precise mechanisms underlying how prefrontal and amygdala neurons encode social gaze events remain elusive. To address this gap, we investigated neuronal correlates of social gaze using a live gaze interaction paradigm, in which we can study spontaneously occurring gaze interactions between pairs of rhesus macaques. We recorded single-neuron and local field potential activity from three prefrontal structures - the anterior cingulate gyrus (ACCg), the orbitofrontal cortex (OFC), and the dorsomedial prefrontal cortex (dmPFC) - and BLA, in order to investigate the contribution of each brain region, as well as the coordination between each of the prefrontal regions and the BLA, in guiding social gaze. We aligned the neuronal data to two types of spontaneous social gaze events - 1) looking at the partner's eyes, and 2) mutual gaze to the eyes by both monkeys (mutual eye contact). We observed notable heterogeneities in the temporal dynamics of spiking activity. Moreover, proportions of significantly modulated cells that differentiated looking at the

eyes from looking at the other parts of the face changed around the time of the gaze event. Similarly, the proportion of a sub-group of these cells that significantly differentiated mutual eye contact from non-mutually looking at the eyes also changed around the time of the gaze event. Furthermore, when the monkey looked at the partner's eyes, compared to the other parts of the face, the coordination between prefrontal areas and BLA exhibited a robust increase in the field-field coherence in the gamma band (50-70 Hz). In contrast, upon mutual eye contact, compared to non-mutually looking at the eyes, we found changes in the coherence not only in the gamma band but also markedly in the low frequency ranges (0-15 Hz). Our findings suggest that various social gaze events are computed across multiple brain regions and their synchrony patterns reflect particular social gaze functions.

Disclosures: O. Dal Monte: None. **S. Fan:** None. **N.A. Fagan:** None. **C.C.J. Chu:** None. **S.W. Chang:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.05/GGG21

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01 MH110750

Title: Tensor component analysis (TCA) of spiking activity related to social gaze dynamics in prefrontal cortex and the amygdala

Authors: *C. C. CHU[1], O. DAL MONTE[1], S. FAN[2], N. FAGAN[2], S. W. CHANG[2]
[1]Dept. of Psychology, [2]Yale Univ., New Haven, CT

Abstract: Human and non-human primates gain critical information about their conspecifics using gaze. However, little is known about how social gaze is computed in the brain. Toward answering this question, we recorded single-neuron and local field potential activity from four different brain regions during spontaneously occurring social gaze interactions (Dal Monte et al., 2016): dorsomedial prefrontal cortex (dmPFC), anterior cingulate cortex gyrus (ACCg), orbitofrontal cortex (OFC), and basolateral amygdala (BLA). We examined how these regions encode social gaze variables by focusing on spiking activity related to looking at the eyes of the partner monkey. Based on the single neurons recorded, we found that each region exhibited heterogeneous temporal dynamics relative to the time of looking at the eyes of the conspecific partner (see Dal Monte et al., 2018 SfN abstract). To better characterize population spiking dynamics, we applied the tensor component analysis (TCA) - a dimension reduction method based on canonical polyadic decomposition, which unfolds neural responses to neuron, time, and trial dimensions (Williams, AH et al., 2017). Whereas TCA indicated that dmPFC modulates its

firing rates in a manner that is time-locked to when monkeys looked at the partner's eyes, BLA exhibits both excitatory and suppressive rate modulation patterns mostly after the onset of this social gaze event. Furthermore, TCA revealed that OFC modulates firing rates on a longer time scale around the same social gaze event. Notably, ACCg exhibits oscillations and rate modulations after looking at the partner's eyes. These TCA results mirrored the neural features observed using Principal Component Analysis (PCA) of the same data. Overall, TCA and PCA analyses suggest that amongst the four brain regions we sampled, each exhibits different time-locked modulations of neural features (rate and oscillation) during social gaze. Overall, TCA provides a useful tool to characterize complex neuronal dynamics. **Reference** Williams, Alex H., Tony Hyun Kim, Forea Wang, Saurabh Vyas, Stephen I. Ryu, Krishna V. Shenoy, Mark Schnitzer, Tamara G. Kolda, and Surya Ganguli. "Unsupervised discovery of demixed, low-dimensional neural dynamics across multiple timescales through tensor components analysis." *bioRxiv* (2017): 211128. Olga Dal Monte, Matthew Piva, Jason A. Morris, and Steve W. C. Chang. "Live interaction distinctively shapes social gaze dynamics in rhesus macaques." *J Neurophysiol* 116: 1626-1643, 2016.

Disclosures: C.C. Chu: None. **O. Dal Monte:** None. **S. Fan:** None. **N. Fagan:** None. **S.W. Chang:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.06/GGG22

Topic: H.01. Animal Cognition and Behavior

Support: UConn - Institute for Brain and Cognitive Sciences
UConn - Science of Learning and Art of Communication

Title: Observation learning in rats: Effect of strain and hormonal status

Authors: *R. TROHA, J. WANG, T. SHAO, E. MARKUS
Univ. of Connecticut, Storrs, CT

Abstract: Observational, or imitative, learning is a vital skill for survival. This type of social learning plays an important role in human development. Albert Bandura's seminal research showed that children which observe an adult interact with a doll in a certain manner will behave in a similar manner with the doll later on. However, observational learning is also important for other species. For example, consider a rat in a new environment and does not know where to find food. A rat that can learn a food location by observing a conspecific finding food is more likely to survive in its environment than a rat which does not learn through observation.
We have developed an observational learning paradigm in which rats must learn the location of

food in a T-shaped maze through observation. This is a working memory task with the correct goal changing on a daily basis. Therefore, the observer must attend to the demonstrator rat's performance on a daily or continuous basis.
Female F344 rats can be trained to use observational learning on this task. However they exhibit observational learning only when the demonstrator rat is near them but not they are observing from a distance. Furthermore there was no effect of the how familiar they were with the demonstrator rat.
Previous research suggests that during the proestrous stage of the rat estrous cycle, there is an increase in both estrogen and oxytocin in the brain. Oxytocin is known to play a role in mediating social and bonding behaviors in rodents.
To explore these issues further we trained female Long Evans Hooded rats on this task. These animals have a better visual acuity than F344. In addition we tracked their estrous cycle to determine hormonal effects on the degree of observational learning.

Disclosures: R. Troha: None. **J. Wang:** None. **T. Shao:** None. **E. Markus:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.07/GGG23

Topic: H.01. Animal Cognition and Behavior

Support: UConn - Institute for Brain and Cognitive Sciences
UConn - Science of Learning and Art of Communication

Title: Observational learning in rats: Effects of number and quality of observations

Authors: *E. J. MARKUS[1], R. TROHA[2], D. DONG[3], N. HERNANDEZ[2], T. SHAO[2]
[1]Univ. of Connecticut, Storrs Manfld, CT; [2]Univ. of Connecticut, Storrs, CT; [3]Univ. of Connecticut, South Windsor, CT

Abstract: Observational learning is an important skill for survival. This type of social learning plays a central role in human development (e.g. Bandura) and observational learning deficits have been linked to disease states such as autism and schizophrenia. Observational learning is also relevant for other species. Learning from the trial and error of others is more efficient than searching yourself when foraging the environment for food. It is also "safer" to acquire information regarding locations of danger in the environment by watching where conspecifics are threatened and how they may/may-not escape the danger.
Previous studies of observational learning have focused on multiple observations of a fixed solution to a problem (e.g. tool use, goal location). The current paradigm differs in that the solution changes across days, requiring the rat to attend daily to the "current solution".

Specifically F344 rats observe a demonstrator rat find the goal arm in a T-shaped maze, with the rewarded arm changing in a pseudorandom fashion.
The observer rats showed better than chance choices on their first trial on the maze. Factors such as the proximity to the demonstrator rat, number of observed trials, quality of the observed trials, and previous experience all determined the performance of the observing animal. The identity of the demonstrator and quality and number of observations from a distance has less of an impact on performance.

Disclosures: E.J. Markus: None. **R. Troha:** None. **D. Dong:** None. **N. Hernandez:** None. **T. Shao:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.08/GGG24

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01 MH104602-01
HHMI

Title: Dual gating by vasopressin of hippocampal CA2 soma and presynaptic terminals in lateral septum

Authors: *F. LEROY[1], L. M. BOYLE[1], J. PARK[1], A. ASOK[2], D. H. BRANN[1], T. MEIRA[1], E. W. BUSS[1], E. R. KANDEL[2], S. A. SIEGELBAUM[1]
[1]Dept. of Neurosci., Columbia Univ., New York, NY; [2]Dept. of Neurosci., Columbia Univ. / HHMI, New York, NY

Abstract: Although the hippocampus is well known to play a central role in declarative memory, its importance for motivated behaviors, including social aggression, remains relatively unexplored. We find that hippocampal CA2 pyramidal neurons, previously implicated in social memory storage, promote social aggression through output to a lateral septal circuit that disinhibits neurons in the ventral medial hypothalamus, which triggers attack on a conspecific. *In vivo* fiber-photometry revealed enhanced CA2 activity during social encounters, with a selective increase in CA2 output to LS preceding attacks. Here we address how a single hippocampal subregion can control both social memory and social aggression. Are there dual populations of CA2 neurons, one projecting to CA1 to mediate social memory and one to LS to promote aggression? Or might a single CA2 population differentially elicit aggression versus social exploration as a result of the internal state of the animal? In dual tracer analysis we now find that most, if not all, CA2 pyramidal neurons bifurcate to project to both CA1 and LS. This suggests that CA2 output may be gated by a neuromodulator whose release depends on internal state. We

focused on the social neuropeptide arginine vasopressin (AVP) as it is known to promote aggression and social memory, and CA2 PNs are highly enriched in the vasopressin 1b receptor (AVPR1b). We hypothesized that the source of vasopressin input to the LS (bed nucleus of the stria terminalis and/or medial amygdala) might differ from the AVP input to dorsal hippocampus (hypothalamic paraventricular nucleus), suggesting the presence of parallel bottom-up and top-down modulatory circuits regulating social aggression and social memory. Our initial results confirm these dual sources of vasopressin input and we are examining their differential control over social memory or social aggression. Furthermore, we show that AVP enhances social aggression by acting on AVPR1b on CA2 presynaptic terminals in lateral septum to enhance excitatory synaptic transmission. In this manner, vasopressin release in lateral septum may serves as a gate driven by an animal's internal state that enables a single brain region to either store declarative memory of a social encounter or promote motivated social aggression.

Disclosures: F. Leroy: None. **L.M. Boyle:** None. **J. Park:** None. **A. Asok:** None. **D.H. Brann:** None. **T. Meira:** None. **E.W. Buss:** None. **E.R. Kandel:** None. **S.A. Siegelbaum:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.09/GGG25

Topic: H.01. Animal Cognition and Behavior

Support: This research was supported by the intramural research program of the NIMH (ZIA-MH-002498-24).

Title: Social memory encoding by Vasopressin 1b receptor-expressing Pyramidal neurons in CA2 hippocampal subfield of mice

Authors: *A. CYMERBLIT-SABBA[1], M. STACKMANN[1], S. K. WILLIAMS AVRAM[1], M. C. GRANOVETTER[1], A. SMITH[2], H.-J. LEE[3], J. SONG[1], W. YOUNG III[1]
[1]NIMH, Bethesda, MD; [2]Dept. of Pharmacol. & Toxicology, Univ. of Kansas, Lawrence, KS; [3]Microbiology & Immunol., Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: Recognitions of others may occur at different levels: social hierarchical status, health (e.g., parasitic load), emotions (e.g., stress-empathy), genetic relatedness (kin recognition) familiarity (have I met you before?) and individual identity (yes, you are Alma) (Colgan, 1983). To maintain successful complex social behaviors, the neural network must allow dynamic acquisition, representation and retrieval of the social cues. The involvement of the CA2 subfield of the hippocampus in social memory have been well established. Still, the way these memories are encoded by it remains, for the most part, unknown. We imaged the calcium transients in selective pyramidal neurons within the CA2 subfield - those that express cre from the Avpr1b

promoter in a mouse knockin line to activate virally delivered GCaMP - of socially behaving mice to map the neural response to the stimuli presented. Our results show increased response upon presentation of a novel stimulus with a subsequent decrease when the stimulus is removed from the cage. Moreover, upon familiarization, neural representation becomes sparser and activity is attenuated in a stimulus-specific manner. Although the cells response to both social and non-social stimuli, the population response is significantly greater when the social stimulus is presented. Our preliminary results suggest a preferred social encoding by these vasopressin 1b receptor-expressing pyramidal neurons, with a possible mechanism of repetition suppression.

Disclosures: A. Cymerblit-sabba: None. **M. Stackmann:** None. **S.K. Williams Avram:** None. **M.C. Granovetter:** None. **A. Smith:** None. **H. Lee:** None. **J. Song:** None. **W. Young III:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.10/GGG26

Topic: H.01. Animal Cognition and Behavior

Support: 2T32MH067564
MH078064

Title: Oxytocin receptor-positive dentate neurons mediate the effects of state-dependent memory on social behavior

Authors: *M. MEYER[1], K. NISHIMORI[2], J. RADULOVIC[3]
[1]Northwestern Univ. - Chicago, Chicago, IL; [2]Grad Sch. of Agric Sci, Tohoku Univ., Sendai-Shi, Japan; [3]Psychiatry & Behavioral Sci., Northwestern Univ., Chicago, IL

Abstract: Stress-related memories are typically encoded so that they can be retrieved robustly. However, under certain conditions, memories cannot be retrieved by natural recall cues, unless the brain is in the same state as during encoding. Such ‘state-dependent’ memories, have been implicated in several psychopathologies, including traumatic amnesia. For instance, patients suffering from stress-related disorders commonly have dissociative symptoms related to their inability to recall the traumatic event unless they are in a similar psychological or physiological state as when the trauma occurred. Despite inaccessibility to retrieval under normal conditions, state-dependent memories may subsequently affect other behaviors, as dissociative amnesia is highly correlated with deficits in social functioning. We therefore investigated phenotypic effects of state-dependent memory on social behavior in mice. In a pharmacological model of state-dependent memory, we demonstrated that state-dependent contextual fear conditioning impairs sociability and social recognition. Based upon accumulating evidence that hippocampal oxytocin

receptors are required for social recognition, but not sociability behavior, we used chemogenetic approaches to test the role of oxytocin receptor-positive neurons in the effects of state-dependent memory on social behaviors. Our experiments demonstrated that oxytocin receptor-positive dentate neurons mediate the observed sociability deficit, such that chemogenetic inactivation successfully rescues behavior. These studies begin to elucidate cellular mechanisms by which state-dependent memories affect social behaviors.

Disclosures: M. Meyer: None. **K. Nishimori:** None. **J. Radulovic:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.11/GGG27

Topic: H.01. Animal Cognition and Behavior

Support: NIH NS065027-01
NIH HD074418-01
NIH T32-NS007441
Rettsyndrome.org
Rett Syndrome Research Trust
Civitan International

Title: Ventral hippocampal inputs to the mPFC regulate social memory

Authors: *M. PHILLIPS[1], L. POZZO-MILLER[2]
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Neurobio., Univ. Alabama-Birmingham, Birmingham, AL

Abstract: Altered ventral hippocampal (vHIP) input to the medial prefrontal cortex (mPFC) has been implicated in many disorders including autism, schizophrenia, and PTSD. Here we use *Mecp2* knockout (KO) mice as a model of the autism-associated disorder Rett syndrome to define the behavioral consequences of altered vHIP-mPFC projections. We first identified an increased influence of vHIP afferents on mPFC network activity in *Mecp2* KO mice when compared to wildtype (WT) littermates, as determined by larger and wider spreading voltage sensitive dye (VSD) signals during subthreshold synaptic potentials evoked by stimulation of vHIP fibers in mPFC slices. To identify active neurons during specific behavioral tasks, we performed retrobead tracing to label pyramidal neurons in the vHIP that project to the mPFC, followed by c-Fos immunohistochemistry as a surrogate of neuronal activity. This approach revealed that mPFC-projecting vHIP neurons are selectively activated in WT and *Mecp2* KO mice during social tasks, compared to non-social tasks and to other vHIP projection neurons. Using unbiased machine-learning classifiers to score behaviors in freely moving mice, we

identified social memory deficits in *Mecp2* KO mice. To test if stronger vHIP inputs to the mPFC are causal to social memory deficits in *Mecp2* KO mice, we altered the activity of mPFC-projecting vHIP neurons by intersectional chemogenetics. Increasing the activity of mPFC-projecting vHIP neurons between P34-P45 with an excitatory DREADD impaired social memory in WT mice. In addition, this manipulation resulted in larger vHIP-evoked VSD signals in mPFC slices, resembling those in *Mecp2* KO mice. On the other hand, reducing the activity of mPFC-projecting vHIP with an inhibitory DREADD was sufficient to restore social memory in *Mecp2* KO mice, while reducing vHIP-evoked VSD signals in mPFC slices, resembling responses in WT mice. Further analyses revealed that the amplitude of vHIP fiber-evoked VSD signals in mPFC slices of inhibitory DREADD-expressing *Mecp2* KO mice correlate with their performance in social memory tasks. These data demonstrate that the vHIP-mPFC projection is necessary for social memory.

Disclosures: M. Phillips: None. **L. Pozzo-Miller:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.12/HHH1

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

Title: Socially learned food preferences are associated with sex-specific changes in dorsal hippocampal dopamine release in mice

Authors: *R. MATTA, M. J. RUSSELL, C. L. LIMEBEER, L. A. PARKER, E. CHOLERIS
Dept. of Psychology and Neurosci. Program, Univ. of Guelph, Guelph, ON, Canada

Abstract: Social learning allows animals the ability to exploit the ‘expertise of others’ to possibly avoid some of the risks that are often associated with trial-and-error individual learning. One form of social learning, often studied in the lab, is the social transmission of food preferences (STFP). Our previous work using systemic treatments of dopamine (DA) receptor antagonists has shown an involvement of DA D1-type receptors in social learning (but not food intake), and DA D2-type receptors in food intake (but not social learning) in the STFP in female mice (Choleris et al., 2011). We are now examining the potential brain region(s) underlying these effects. Dopaminergic projections ascend from the ventral tegmental area (VTA) to many limbic brain structures, including the hippocampus, which has been established as necessary for the initial encoding/acquisition of the STFP in rodents. Our previous work using DA receptor antagonists infused directly into the dorsal hippocampus has shown that female mice rely on both DA D1- and D2-type receptors, while male mice only rely on DA D1-type receptors (Matta et

al., 2016, 2017). In this study we examined whether social learning in the STFP was associated with changes in dorsal hippocampal DA release in male and female mice. This study involved the use of *in vivo* microdialysis sampling (flow rate of 0.6 μL/min, samples collected every 20 min), and high-performance liquid chromatography (HPLC) detection of dopamine. We found that both females and males acquired a socially learned food preference and there were no sex differences in total food intakes. Females and males also spent more time investigating a socially demonstrated/learned (DEM) diet odor than a NON-DEM diet odor. Direct comparisons between males versus females showed that hippocampal DA release during the NON-DEM diet odor (novel food), NON-DEM social (no social learning), and STFP was greater for males than females. Comparisons directly to baseline samples further showed that male hippocampal DA release increased during the NON-DEM diet odor, NON-DEM social, STFP exposure, and choice test. On the other hand, female hippocampal DA release decreased during the NON-DEM diet odor, NON-DEM social, and STFP exposure. Notably, there was no difference between female vs. male oronasal investigation durations during the STFP, suggesting that the sex differences in dorsal hippocampal DA release during STFP could not be explained by differences in exposure to the socially carried food odor found on the breath of the DEM. Together, the current and our previous findings suggest sex-specific mechanisms in dorsal hippocampal DA mediation of social learning.

Disclosures: R. Matta: None. **M.J. Russell:** None. **C.L. Limebeer:** None. **L.A. Parker:** None. **E. Choleris:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.13/HHH2

Topic: H.01. Animal Cognition and Behavior

Support: University of Colorado Boulder
Whitehall Foundation Grant
Colorado Clinical and Translational Sciences Institute CNS Pilot Grant
R00 MH102352

Title: Delineating the hippocampal circuitry underlying pair bonding in prairie voles

Authors: *J. A. TEMPLE[1], M. A. BEST[1], H. R. DOUGHERTY[1], Z. R. DONALDSON[2]
[1]Univ. of Colorado Boulder, Boulder, CO; [2]MCBD/Psychology & Neurosci., Univ. of Colorado, Boulder, Boulder, CO

Abstract: Pair bonds are long-lasting social attachments that form between mating partners. While pair bonding is common among humans, the majority of mammals, including laboratory

rats and mice, do not exhibit this trait. Instead, socially monogamous prairie voles, which form life-long pair bonds, provide an excellent model for studying attachment in adults. To date, the study of pair bonding in prairie voles has focused on neuromodulatory systems, including oxytocin, vasopressin, dopamine and endogenous opiates, while the specific neural circuits that modulate attachment remain largely unexplored. The ventral hippocampus has been implicated in regulation of emotions and social memory across a variety of rodent species. Thus, we asked whether the ventral hippocampus is required for a selective partner preference, a behavioral indicator of pair bonding. We used ibotinic acid to bilaterally lesion the ventral CA1 region in female prairie voles. After two weeks of recovery, estrogen-primed females were paired and mated with a male. Twenty-four hours later, we performed a partner preference test, which revealed that lesion animals failed to form a preference, while sham animals exhibited a strong preference for their mate. Our ongoing work is examining the specific role of different hippocampal projections in different phases of pair bonding. This research will provide a novel dissection of the role of hippocampal systems in pair bonding behavior, potentially providing valuable insights into how disruption of these circuits contributes to social deficits.

Disclosures: J.A. Temple: None. **M.A. Best:** None. **H.R. Dougherty:** None. **Z.R. Donaldson:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.14/HHH3

Topic: H.01. Animal Cognition and Behavior

Support: NIH-NINDS Training Grant 5 T32 NS 064928-08
NIH 1 R01 NS106983-01
NIH R21 NS093991

Title: Exploring the role of hippocampal area CA2 in the pilocarpine mouse model of mesial temporal lobe epilepsy

Authors: *A. WHITEBIRCH[1], K. S. VADDURI[2], B. SANTORO[2], S. A. SIEGELBAUM[2]
[1]Neurosci., Columbia Univ., New York, NY; [2]Dept of Neurosci., Columbia Univ. Coll P & S, New York, NY

Abstract: Mesial temporal lobe epilepsy (MTLE) is a drug-resistant form of epilepsy associated with a pattern of pathology termed mesial temporal sclerosis, in which there is extensive cell loss in hippocampal areas CA1 and CA3 while the dentate gyrus and CA2 regions remain relatively intact. The fact that the hippocampus is a major site of seizure activity in MTLE, despite the degeneration in CA1 and CA3, suggests that epileptiform activity may be generated in or

conveyed through surviving CA2 circuitry. Accumulating evidence suggests that CA2 may have a key role controlling hippocampal network excitability in the healthy brain, but CA2 circuits have not been well-characterized at a physiological level. CA2 pyramidal neuron (PN) axons form local collaterals and project throughout the hippocampus, contributing to a recurrent excitatory network that generates both normal and pathological forms of synchronous activity. Despite anatomical evidence, recurrent connectivity among CA2 PNs has not been investigated electrophysiologically. Back-projecting axons from CA2 are known to evoke direct excitatory and feedfoward inhibitory responses in CA3, but the role of this circuit in MTLE has not been investigated. Importantly, changes to CA2 excitability or functional synaptic connectivity in epileptic mice and the contribution of CA2 to hippocampal hyperexcitability remain unexplored. To address these gaps in knowledge, I use optogenetic and chemogenetic approaches in the *Amigo2-Cre* mouse line to selectively target CA2 PNs. This targeted approach enables characterization both of CA2 circuits in normal tissue and of alterations to CA2 intrinsic and extrinsic electrophysiological properties in the pilocarpine mouse model of MTLE. I hypothesize that in MTLE area CA2 acts as a hub supporting the generation and propagation of epileptiform activity in the hippocampal network. My preliminary data from normal mice suggest that CA2, like CA3, is part of an auto-associative network. Thus, CA2 PNs send longitudinal connections that excite other CA2 neurons. As reported by others, CA3 excitation by CA2 is normally limited by strong feed-forward inhibition. Data from pilocarpine-treated mice reveal increased intrinsic excitability of CA2 PNs and suggest enhanced excitatory synaptic input to CA2 as a result of decreased feedforward inhibition. Furthermore, in an *in vitro* model of pharmacologically-induced epileptiform activity, acute silencing of CA2 PNs reduced population bursting in CA1. Moving forward, this research will advance our understanding of the role of CA2 in the generation of seizures in MTLE, one of the most common and difficult to treat forms of focal epilepsy.

Disclosures: A. Whitebirch: None. **K.S. Vadduri:** None. **B. Santoro:** None. **S.A. Siegelbaum:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.15/HHH4

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH106629
NSF DGE-16-44869

Title: Modified firing in hippocampal area CA2 in a mouse model of schizophrenia during social tasks

Authors: *M. L. DONEGAN[1], F. STEFANINI[1], S. FUSI[1], J. A. GORDON[2], S. A. SIEGELBAUM[3]
[1]Neurosci., Columbia Univ., New York, NY; [2]Office of the Director, Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Dept of Neurosci., Columbia Univ. Coll P & S, New York, NY

Abstract: Social interaction and bonding are crucial for mammalian survival, providing a support system for offspring rearing, increased security, and reduced expenditure of resources. Recent work on area CA2 of the hippocampus has shown it is necessary for the formation of social memory, and that optogenetic stimulation of neuromodulatory inputs to CA2 improves social memory. CA2 has also been implicated in neuropsychiatric diseases associated with altered social behavior. Thus, patients with schizophrenia and bipolar disorder show specific losses of parvalbumin-positive (PV+) interneurons in CA2 but not neighboring CA1 and CA3. Of particular interest, these alterations in CA2 are recapitulated in the Df(16)A+/- mouse model of the 22q11.2 deletion syndrome, which confers a 30-fold increased likelihood of developing schizophrenia in humans. Thus, these mice show an age-dependent loss of PV+ interneurons specific to CA2, as well as a deficit in social memory. CA2 pyramidal neurons also become hyperpolarized in these mice via an upregulation of the TREK-1 outward rectifying potassium channel. Although CA2 has been implicated in social memory and its disorders, little is known about the normal in vivo firing properties of CA2, and how these may be altered in disease. To characterize CA2 firing during social behavior we recorded extracellularly from CA2 of both wild-type and Df(16)A+/- mice during a modified 3 chamber social interaction task during which the mice interact with: 1) an empty chamber, 2) novel objects, 3) littermates, and 4) novel mice. In wild-type animals, CA2 firing is highly heterogeneous during this task, and CA2 spatial firing is diffuse and unstable from session to session. CA2 pyramidal cells from Df(16)A+/- mice show no change in average or peak firing rates during these tasks, suggesting that the hyperpolarization and reduced inhibition may be compensatory. However, CA2 firing patterns of Df(16)A+/- mice are significantly more stable across the different sessions, with greater spatial information content. CA2 population activity in wild-type mice is better able to decode the context in a session—for example, whether a mouse is in a social versus non-social session—compared to neurons from Df(16)A+/- mice. These results indicate that changes in firing patterns of hippocampal area CA2 are necessary for social memory, and the increased stability of CA2 firing patterns may contribute to social deficits associated with neuropsychiatric diseases such as schizophrenia.

Disclosures: M.L. Donegan: None. **F. Stefanini:** None. **S. Fusi:** None. **J.A. Gordon:** None. **S.A. Siegelbaum:** None.

Poster

691. Animal Cognition and Behavior: Social Memory and Cognition II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 691.16/HHH5

Topic: H.01. Animal Cognition and Behavior

Support: NRF-2017R1D1A1B05036195

Title: Correlations of autism-like behaviors and altered hippocampal circuit following febrile seizures

Authors: *Y. YU, J. KANG, K. LEE, D.-Y. YOO, D.-K. PARK, K.-H. PARK, D.-S. KIM
Col. of Med., Soonchunhyang Univ., Cheonan-Si, Chungcheongnam-Do, Korea, Republic of

Abstract: Febrile seizure (FS) is the most common seizure type in the infant and young child. FS induce functional changes in the hippocampal circuitries and then contributed toward the development of temporal lobe epilepsy (TLE). Moreover, the hippocampus is critical for encoding declarative memory and especially, dysfunction of CA2 pyramidal neurons caused a pronounced loss of social memory in genetic and autism models. On the other hand, autism is a neurodevelopmental disorder characterized by deficits in social interaction, restricted and repetitive behaviors. Therefore, in this study, we are identifying the interrelation that autism-like behavior and dysfunction hippocampal circuits in FS animal model. In the results of this study, to characterize of behavioral disturbance by emotional, social and cognitive dysfunction, we were experimented behavior test. In addition, we were investigated field excitatory postsynaptic potential (fEPSP) in the hippocampus for identifying impairs synaptic transmission, observed that resultant slope of fEPSP were markedly reduced more than control level. Additionally, immunoreactivity of interleukin-6 (IL-6) was enhancing those CA2 regions of hippocampus and cerebellum compared with control. Therefore, our findings in present study revealed that autistic neuroanatomical structures and neuronal plasticity in development periods after FS, thus it might seem to be involved to potential onset of autism by genetic alterations following FS.

Disclosures: Y. Yu: None. **J. Kang:** None. **K. Lee:** None. **D. Yoo:** None. **D. Park:** None. **K. Park:** None. **D. Kim:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.01/HHH6

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1R15AG045820-01A1

Title: Maturation of excitatory synapses studied in parallel with spatial navigation ability in the juvenile rat

Authors: *N. VALIBEIGI[1], C. KIMBALL[2], D. CHEN[4], R. H. OGOE[5], D. G. MCHAIL[2], T. C. DUMAS[3]
[1]Krasnow Inst. for Advanced Study, Fairfax Station, VA; [3]Psychology, [2]George Mason Univ., Fairfax, VA; [4]Krasnow Inst., Vienna, VA; [5]Krasnow Inst., Fairfax, VA

Abstract: Spatial navigation in rodents depends on neural networks in the hippocampus, a forebrain structure known for its role in human episodic memory. This critical ability emerges at about three weeks of age [postnatal day, (P)21] in rodents, in parallel with functional changes at hippocampal excitatory synapses. In particular, hippocampal AMPA receptors shift in composition from predominantly GluA1-containing to GluA3-containing, and this prolongs the synaptic response and lowers the threshold to induce long-lasting changes in synaptic strength. In prior research, we demonstrated that treatment of juvenile rats with AMPAKINE drugs, which prolong excitatory synaptic responses, elicited more mature spontaneous alternation in a Y-maze. Since free exploration in the Y-maze does not have distinct learning and memory phases, we adapted the Barnes maze task for juvenile animals. We explored relationships between AMPAR subunit expression and spatial learning and memory abilities in juvenile Long Evans rats just under (P17-20) and just over three weeks (P22-25). Half of the animals at each age were treated with AMPAKINE drug before Barnes maze testing and double immunofluorescent labeling (GluA1, GluA3) was performed on thin brain sections from maze trained animals and naïve controls. It was found that while AMPAKINE delivery did not affect learning at either age, older animals treated with AMPAKINE showed a more direct approach to the goal location in memory probes than older control animals. Ongoing analyses will assess whether developmental differences in AMPAR subunit expression are related to maze performance. Together, the results will help clarify what aspects of spatial learning and/or memory are impacted by maturation of hippocampal AMPARs

Disclosures: N. Valibeigi: None. **C. Kimball:** None. **D. Chen:** None. **R.H. Ogoe:** None. **D.G. McHail:** None. **T.C. Dumas:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.02/HHH7

Topic: H.01. Animal Cognition and Behavior

Title: NYX-458, a novel small molecule NMDA receptor modulator, enhances novel object recognition in rats

Authors: *E. M. COLECHIO[1], T. K. BHATTACHARYA[2], J. AGUADO[2], J. GAJDA[2], A. BARTH[2], E. RODRIGUEZ[2], P. KANSARA[2], E. POLLARD[2], M. A. KHAN[3], P. K. STANTON[4], X. L. ZHANG[4], M. S. BOWERS[2], J. R. MOSKAL[2], C. N. CEARLEY[2]

[1]Behavioral Pharmacol., Aptinyx, Inc., Evanston, IL; [2]Aptinyx Inc, Evanston, IL; [3]Aptinyx, Inc, Evanston, IL; [4]Cell Biol. & Anat., New York Med. Col., Valhalla, NY

Abstract: Aptinyx has developed a novel class of small molecule N-Methyl-D-aspartic acid receptor (NMDAR) modulators with broad applicability across neurologic and psychiatric disorders. Aptinyx compounds display differential binding to NMDARs containing the A, B, C, or D NMDAR2 subtypes. Using the [3]MK-801 potentiation assay with HEK cell membrane extracts containing specific NMDAR2 subtypes, we found that NYX-458 binds the B and D, but not A or C subtypes. Given the central role of NMDARs in synaptic plasticity, NYX-458 effect on long-term potentiation (LTP) was evaluated. NYX-458 was found to enhance the magnitude of LTP at Schaffer collateral/CA1 hippocampal synapses when applied to slices at 100 nM. Given this, we tested the hypothesis that NYX-458 would facilitate cognition using the NOR assay. This assay is based on rats' instinctive preference for exploring novel objects, stimuli, and environments and is considered a measure of recognition memory. Administration of NYX-458 (0.01, 0.1, 1, or 10 mg/kg, PO) 1 h before the sample trial (T1) increased exploration of the novel object relative to the familiar object in the test trial (T2) conducted 24 h later. Further studies demonstrated that the effect was only seen when compound was administered prior to T1 and not when administered either immediately following T1, or 1 h before T2, suggesting that NYX-458 selectively facilitates encoding of object recognition versus consolidation or retrieval. Studies were also performed to better understand the duration of effect and a single dose of NYX-458 (0.1 mg/kg, PO) improved object recognition memory when administered up to 48 h before T1 and continued to be effective when the T1-T2 intertrial interval was extended to 48 h. Additional pharmacokinetic and safety pharmacology studies showed that NYX-458 exhibited high oral bioavailability and brain penetrance, with no psychotomimetic or locomotor effects seen in either open field or Rota-rod assays. Together, these data indicate that NYX-458 is a novel, well-tolerated, orally bioavailable NMDAR modulator that exhibits pro-cognitive effects.

Disclosures: E.M. 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. **T.K. Bhattacharya:** 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. Aguado:** 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. Gajda:** 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. Barth:** 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. Rodriguez:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); APTINYX, INC. **P. Kansara:** 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. Pollard: 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. **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. **P.K. Stanton:** F. Consulting Fees (e.g., advisory boards); APTINYX, INC. **X.L. Zhang:** F. Consulting Fees (e.g., advisory boards); APTINYX, INC. **M.S. Bowers:** 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. **C.N. 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.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.03/HHH8

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant: R-43AG051299-01

Title: NYX-458, a NMDA receptor modulator, when tested in aged F344 rats, facilitates LTP and reverses age-related cognitive deficits as measured by the Morris water maze

Authors: *A. L. BARTH[1], J. D. AGUADO[2], A. MOGHADAM[4], P. K. STANTON[5], M. A. KHAN[1], J. R. MOSKAL[6,3], C. CEARLEY[2]
[1]Aptinyx Inc, Evanston, IL; [2]Res., [3]Aptinyx Inc., Evanston, IL; [5]Cell Biol. & Anat., [4]New York Med. Col., Valhalla, NY; [6]Northwestern Univ., Evanston, IL

Abstract: Aptinyx has developed a novel class of small molecule orally bioavailable N-methyl-D-aspartate receptor (NMDAR) modulators with broad applicability across CNS disorders. NYX-458 has a preference for NMDAR2B and NMDAR2D receptor subtypes and shows cognitive enhancement in rodent learning models with no toxicity or safety pharmacology concerns at all doses tested. In the present study, NYX-458 was initially evaluated for effect on aged F344 (26-27 months-old) rat hippocampal long-term potentiation (LTP) and long-term depression (LTD). NYX-458 was then evaluated in aged F344 rats tested in the Morris water maze (MWM) for efficacy in treating age-related cognitive decline.The magnitude of stimulus-evoked LTP in aged F344 rat was markedly reduced relative to young adult (3 month old F344)

rats. Bath application of NYX-458 (50 and 100 nM) to hippocampal slices in vitro from aged rats was shown to enhance the magnitude of long-term potentiation (LTP) at Schaffer-collateral-CA1 synapses to levels seen in young adult rats. LTD at hippocampal Schaffer-collateral-CA1 synapses and was not significantly different in aged rats from young adult rats. NYX-458 (50, 100 and 500 nM) had no effect on LTD in either young adult or aged rats. Lastly, we assessed NYX-458 (0.1, 1, and 10 mg/kg, PO) for effect on aged rat performance in the fixed platform version of the MWM. In these assays, young rats, when released twice per day from four equally spaced starting positions around the perimeter of the pool (in a pseudorandom order to prevent a procedural learning strategy), were able to use extra-maze cues to locate a hidden circular platform that remained in the same location across all 4 training days. Unlike young rats, aged rats did not show improvements in performance (as measured by reductions in path length, latency to the platform, and Gallagher's measure) across all 4 training days. Importantly, administering NYX-458 (1 mg/kg) at 1 hour prior to the start of testing on each day, brought aged rat performance to young rat performance levels by day 4. Taken together, these data suggest that NYX-458 enhances synaptic plasticity mechanisms associated with learning and memory and has therapeutic potential for treating age-related cognitive decline.

Disclosures: A.L. Barth: 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.D. Aguado:** 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. **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. **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. **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..

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.04/HHH9

Topic: H.01. Animal Cognition and Behavior

Support: Research grant for young scientists YS15_2.3.1_34 Shota Rustaveli National Science Foundation

Title: Neuroprotective effects of chronic memantine treatment on okadaic acid (ICV) induced neurotoxicity at behavioral, structural and molecular level in rats

Authors: *G. BESELIA[1,2], M. DASHNIANI[1], M. BURJANADZE[1], N. CHKHIKVISHVILI[1], L. KRUASHVILI[1], M. CHIGLADZE[1]
[1]Lab. of Behavior and Cognitive Functions, I. Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia; [2]Dept. of Behavioral Sci., Petre Shotadze Tbilisi Med. Acad., Tbilisi, Georgia

Abstract: In the present study, intracerebroventricular (ICV) injection of okadaic acid **(**OA) in rats was used as a memory impairment and hippocampal neurodegeneration animal model. The possible beneficial effect of memantine - NMDA (N-methyl-D-aspartate) receptor antagonist on the OA-induced spatial memory impairment was examined in Morris water maze (MWM). The neuroprotective potential of memantine on OA-induced structural and molecular changes in the hippocampus and medial septum (MS) was evaluated by immuno and Nissl staining. The OA induced neurotoxicity and neuroprotective effects of chronic memantine treatment at behavioral, structural and molecular level was evaluated in 4 groups of animals: control rats injected i.p. with saline or memantine and **OA injected rats** treated i.p. with saline or memantine. OA was dissolved in artificial cerebrospinal fluid (aCSF) and injected ICV 200 ng in avolume of 10 µl bilaterally. Vehicle control received 10 µl of aCSF ICV bilaterally. Memantine (5 mg/kg, i.p) or saline were given daily for 13 days starting from the day of OA injection. Experimental protocol was approved by Animal Studies Committee of I. Beritashvili Center of Experimental Biomedicine. The results described in this chapter showed that bilateral injection of OA causes a deficiency of spatial memory and loss of hippocampal cells in this model and demonstrated for the first time, to our knowledge, reduces the number of cholinergic and GABAergic medial septal neurons. These changes are observed in patients with Alzheimer's disease and, therefore, reinforce the importance of this model for the investigation targets of new therapeutic strategies. The results have shown that the chronic exposure of memantine can prevent a deficiency of spatial memory and that an improvement in memory function correlates with the prevention of OA-induced neuropathological changes in the hippocampus and MS. This fact, on the one hand, points to the involvement of neuropathological processes developed in the hippocampus and MS in memory impairment caused by OA, and, on the other hand, the involvement of NMDA receptors in the neurotoxicity of OA.

Disclosures: G. Beselia: None. **M. Dashniani:** None. **M. Burjanadze:** None. **N. Chkhikvishvili:** None. **L. Kruashvili:** None. **M. Chigladze:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.05/HHH10

Topic: H.01. Animal Cognition and Behavior

Support: NIH DA020041

Title: Dopamine and norepinephrine transporter inhibitors act synergistically to enhance long-term memory

Authors: *M. M. PANTONI, C. DOAN, T. QIU, L. HAMMAM, S. G. ANAGNOSTARAS
Psychology, UC San Diego, La Jolla, CA

Abstract: Psychostimulants (e.g., amphetamine and methylphenidate) are highly effective cognitive enhancers, yet have a high potential for addiction. It is widely believed that norepinephrine transporter (NET) inhibition is exclusively responsible for the procognitive effects of psychostimulants. However, increasing evidence suggests that dopamine transporter (DAT) inhibition is also required for psychostimulant-induced long-term memory (LTM) enhancement. Although DAT inhibition is responsible for the addictive potential of psychostimulants, drugs with weak affinity for DAT may not produce addiction. In the present study, we examined the combined effects of strong NET inhibition (e.g., atomoxetine, nisoxetine) and weak DAT inhibition (e.g., bupropion) on LTM in mice (adult, male and female, n = 8 to 24 per dose group) using Pavlovian fear conditioning. While individually these NET and DAT inhibitors had no effect on LTM across a range of doses, the combination of certain doses significantly enhanced LTM relative to saline controls. Additionally, combined NET and DAT inhibition did not produce reinforcement on a conditioned place preference test. We propose that a pharmaceutical combination of strong NET and weak DAT inhibition could lead to the development of a highly effective cognitive-enhancing medication that lacks the potential for addiction.

Disclosures: M.M. Pantoni: None. **C. Doan:** None. **T. Qiu:** None. **L. Hammam:** None. **S.G. Anagnostaras:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.06/HHH11

Topic: H.01. Animal Cognition and Behavior

Title: Iso-alpha-acids, bitter components in beer, improve memory function via dopaminergic activation in hippocampus

Authors: *Y. ANO[1], A. HOSHI[2], S. UCHIDA[3], K. YAMADA[3], K. KONDO[1]
[1]Res. Labs. for Hlth. Sci. & Food Technologies, [2]Central Labs. for Key Technologies, Kirin Company, Limited, Yokohama, Japan; [3]Kyowa Hakko Kirin Co., Ltd., Shizuoka, Japan

Abstract: Background Our group previously demonstrated that iso-α-acids, bitter components in beer, prevent Alzheimer's disease pathology in the transgenic model mice (Ano et al., 2017), but the effects of iso-α-acids on neuronal activity and memory function have not been elucidated. In the present study, the effect of iso-α-acids on memory function was investigated.Materials and Methods To investigate the effects of iso-α-acids on memory impairment induced by Aβ, the spatial and episodic memories were evaluated by spontaneous alteration test of Y-maze and by novel object recognition test (NORT) at 1 hour after oral administration of donepezil or iso-α-acids in 6-week-old male ICR mice treated intracerebroventricularly with oligomer Aβ1-42. Next, to evaluate in amnesia or normal condition, mice orally given iso-α-acids were subjected to the Y-maze trial after the intraperitoneal injection with scopolamine or to NORT. Besides the behavioral evaluations, for measuring the effects of iso-α-acids on monoamine productions in the brain, the monoamine levels in the hippocampus of SD rats orally administered with iso-α-acids was measured using a microdialysis system. Finally, to determine the involvement of dopamine receptor, mice given iso-α-acids were treated with scopolamine and SCH23390 which is dopamine D1 receptor antagonist before the Y-maze test. Results Intakes of iso-α-acids significantly improved memory impairment of spontaneous alterations in Y-maze and novel object approaching time in Aβ-inoculated mice, which was equivalent to donepezil. A single intake of iso-α-acids also improved the scopolamine-induced amnesia and enhanced episodic memory in normal mice. These results suggest that intakes of iso-α-acids enhance the hippocampus dependent memory function. Microdialysis analysis revealed that an intake of iso-α-acids significantly increased dopamine release in the hippocampus of SD rats compared with control treatment. Treatment with dopamine D1 receptor antagonist attenuated the improvement of spontaneous alteration by iso-α-acids. These results suggest that an intake of iso-α-acids improves memory function via dopaminergic neuronal activation. Conclusion The present study revealed that intakes of iso-α-acids, hop derived bitter components in beer, enhance dopaminergic systems in the hippocampus and spatial and episodic memories. Some reports described that dopamine is involved in the hippocampus dependent memories. Intakes of iso-α-acids might contribute to the improvement of cognitive decline through the activation of memory functions.

Disclosures: Y. Ano: A. Employment/Salary (full or part-time):; Kirin Company, Limited. **A. Hoshi:** A. Employment/Salary (full or part-time):; Kirin Company, Limited. **S. Uchida:** A. Employment/Salary (full or part-time):; Kyowa Hakko Kirin Co., Ltd. **K. Yamada:** A. Employment/Salary (full or part-time):; Kyowa Hakko Kirin Co., Ltd. **K. Kondo:** A. Employment/Salary (full or part-time):; Kirin Company Ltd..

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.07/HHH12

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH068073
Sackler Institute for Developmental Psychobiology

Title: The effects of serotonergic hallucinogens on temporal processing

Authors: *B. AKDOGAN[1], S. DEWIL[1], B. COTTEN[2], A. WANAR[2], J. GINGRICH[1,3], P. D. BALSAM[2,3]
[1]Columbia Univ., New York, NY; [2]Barnard Col., New York, NY; [3]New York State Psychiatric Inst., New York, NY

Abstract: Impairments in temporal processing occur in many psychiatric disorders including schizophrenia. However, despite the fundamental role of timing in adaptive behavior and goal-directed action, the neural substrates of timing deficits observed in schizophrenia are not well-characterized. To begin addressing this question, we targeted the 5-HT_2 receptors which are implicated in timing behavior and in hallucinations, a symptom of schizophrenia. Specifically, we first trained mice in a temporal bisection task in which they learned to categorize durations as short or long. We then administered the hallucinogen 2,5-dimethoxy-4-iodoamphetamine (DOI) at one of three doses (0.3, 1.0, 3.0 mg/kg) prior to test sessions. Systemic DOI injections led to dose-dependent disruptions in mice's duration discrimination performance. Specifically, higher doses of DOI administration flattened and shifted the response functions to the right, indicating that mice were more variable in their temporal choices and had a higher tendency to categorize experienced durations as short. These results corroborate the importance of serotonergic signaling in timing ability and suggest that disruptions in serotonergic signaling in schizophrenia patients may contribute to hallucinations and more generally to an altered sense of reality including changes in temporal information-processing.

Disclosures: B. Akdogan: None. **S. Dewil:** None. **B. Cotten:** None. **A. Wanar:** None. **J. Gingrich:** None. **P.D. Balsam:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.08/HHH13

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant GM083883

Title: Effects of 5-HT6 receptor blockade on repetitive behaviors in the BTBR mouse model of autism spectrum disorder

Authors: *S. PETERSON[1], R. POSADAS[2], A. HERNANDEZ[2], J. DURO[2], D. LOPEZ-SANCHEZ[2], D. A. AMODEO[2]
[1]Psychology, California State Univ. San Bernardino, Upland, CA; [2]Psychology, California State Univ. San Bernardino, San Bernardino, CA

Abstract: Repetitive behaviors are a prevailing symptom across several neuropsychiatric and neurodevelopmental disorders. To date, there is a lack of effective treatments for the attenuation of repetitive behaviors with restricted interests (RRB) in autism spectrum disorder (ASD). The 5-hydroxytryptamine 6 (5-HT6) receptor is of particular interest as a therapeutic target because blockade has been shown to have pro-cognitive affects and is a promising novel target for attenuating behavioral rigidity. The current experiments aim to better determine how the 5-HT6 receptor antagonist BGC 20-761 attenuates repetitive grooming and behavioral inflexibility in the BTBR mouse model of ASD and control C57BL/6J strain. Mice were tested on three separate behavioral measures including the 8-arm spatial strategy task (behavioral flexibility), repetitive grooming (sensorimotor stereotypy) and locomotor activity. Mice received an injection of vehicle, 0.1, or 1 mg/kg BGC 20-761 before each of six consecutive days of testing. Initial experiments demonstrate that vehicle treated BTBR mice show an impairment in the 8-arm spatial strategy task. We predicted that 5-HT6 receptor antagonist treatment would attenuate the behavioral inflexibility expressed by BTBR mice in this particular task. Contrary to our predictions, BGC 20-761 did not attenuate behavioral flexibility in BTBR mice compared to C57BL/6J controls. Current studies are examining the effects of 5-HT6 receptor agonist EMD386088. BGC 20-761 at both 0.1 and 1 mg/kg BGC 20-761 reduced repetitive grooming in the BTBR mouse. Vehicle and BGC 20-761 treated BTBR mice showed comparable locomotor activity. Together these findings suggest that 5-HT6 receptor blockade with BGC 20-761 may be effective at reducing the sensorimotor repetitive behaviors in ASD but may not be effective for the more cognitively-based repetitive choice behavior.

Disclosures: S. Peterson: None. **R. Posadas:** None. **A. Hernandez:** None. **J. Duro:** None. **D. Lopez-Sanchez:** None. **D.A. Amodeo:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.09/HHH14

Topic: H.01. Animal Cognition and Behavior

Support: Killgore Research Grant from West Texas A&M University

Title: Neurobehavioral effects of chronic risperidone administration on juvenile male rats

Authors: *M. F. DE BUTTE, L. BOMAN
Psychology, Sociology, and social work, West Texas A&M Univ., Canyon, TX

Abstract: Despite substantial increases in the use of antipsychotics to treat various psychiatric conditions in children, there is a lack of literature regarding long-term effects of early treatment. Some studies have indicated that early administration results in differential alterations to neurotransmission systems, but few studies have investigated whether there are long-term behavioral modifications. Therefore, the aim of the current study was to investigate the neurobehavioral effects of low dose risperidone (a commonly prescribed antipsychotic) treatment using juvenile rats. Twenty-four male Sprague-Dawley rats were either subcutaneously implanted with a continuous release risperidone pellet (.04 mg/day) or a placebo pellet. To encompass the peri-adolescent to adolescent timeframe (postnatal day 40-60) thought to be important for brain development, male rats began risperidone treatment at post-natal day 35. Six weeks following commencement of risperidone treatment, all rats were tested on a battery of behavioral assessments including open field, object recognition, Morris Water Maze, and Y-Maze spontaneous alternation tasks. Risperidone treatment did not affect open field, object recognition, or Morris Water maze tasks. A significant effect was found on the Y-maze. Although all rats exhibited normal spontaneous alternation, risperidone treated rats demonstrated significantly higher same arm returns, indicative of a working memory deficit. Continued research is needed to determine whether early exposure to risperidone may lead to differences in spatial working memory at longer time-points. These results seem to indicate that early low dose risperidone treatment does not severely impair behavior during the peri-adolescent and adolescent period in rats.

Disclosures: M.F. De Butte: None. **L. Boman:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.10/HHH15

Topic: H.01. Animal Cognition and Behavior

Support: This work was funded by Zogenix Inc.

Title: Fenfluramine is a sigma-1 receptor positive modulator in mice

Authors: *T. MAURICE[1], A. GAMMAITONI[2], B. S. GALER[2], P. MARTIN[2]
[1]INSERM UMR-S1198, Montpellier, France; [2]Zogenix Inc., Emeryville, CA

Abstract: Fenfluramine (*N*-ethyl-α-methyl-3-(trifluoromethyl)-benzeneethanamine, FFA) is a potent serotonin releaser activating multiple 5-HT receptor subtypes. In Dravet syndrome, a

severe epilepsy syndrome starting within the first year of life and due to a de novo mutation ineSCN1A sodium channel in up to 80% of the cases, the drug was recently shown in a Phase 3 trial to have profound (63.9%) greater reduction in mean monthly convulsive seizures compared to placebo ($p<0.001$). Beyond serotonin, FFA also binds to other receptors, particularly showing high nanomolar affinity for the sigma-1 chaperone protein (S1R). In a functional assay, FFA slightly increased the S1R agonist (+)-SKF-10,047-induced increase in the twitch contraction amplitude, suggesting a complex mode of action at S1R. We therefore examined the FFA action at S1R in a functional assay (the S1R/BiP dissociation) and in behavioral responses (forced swimming and two memory tests). Although not explicitly linked to FFA activity in DS, the behavioral responses can provide important insight into FFA mechanism of action. FFA failed to dissociate S1R from BiP in a cell-based assay, but potentiated the S1R agonist PRE-084 effect. FFA, dose dependently but in a bell-shaped manner, attenuated MK-801-induced learning impairments in the spontaneous alternation and passive avoidance tests in mice. In co-administration studies with PRE-084, FFA potentiated the S1R agonist effect and precise calculations of combination indices showed synergy at the lowest doses combination. In addition, the (+)-isomers of both FFA and its metabolite norfenfluramine (NF), showed antidepressant activity in the FST test. Serotonergic receptor antagonists prevented the effect of both (+)-FFA and (+)- NF. The S1R antagonist NE-100 fully prevented only the (+)-FFA effect. These results confirmed a S1R pharmacological component in FFA behavioral effects and both the cell-based assay and the memory tests suggest that the drug behaves as a potent S1R positive modulator, an effect that likely reinforces its known serotoninergic pharmacological actions.

Disclosures: T. Maurice: F. Consulting Fees (e.g., advisory boards); Zogenix Inc. **A. Gammaitoni:** A. Employment/Salary (full or part-time):; Zogenix Inc, Emeryville, CA, USA. **B.S. Galer:** A. Employment/Salary (full or part-time):; Zogenix Inc, Emeryville, CA, USA. **P. Martin:** A. Employment/Salary (full or part-time):; Zogenix Inc, Emeryville, CA, USA.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.11/HHH16

Topic: H.01. Animal Cognition and Behavior

Title: Cognitive enhancement and metabolic effects of Vyvanse in rats

Authors: *H. M. MURPHY[1], C. H. WIDEMAN[2]
[1]Dept Psychol, [2]Dept Biol., John Carroll Univ., University Heights, OH

Abstract: Cognitive enhancers are drugs that improve higher-order mental processes including memory, creativity, focus, and motivation in healthy individuals and psychomotor stimulants are a major class of drugs utilized as cognitive enhancers. Vyvanse (lisdexamfetamine) is classified

as a psychostimulant. It is a prodrug of dextroamphetamine involving a lysine group which is cleaved off through an enzymatic reaction in the blood that liberates the active component. Prodrugs have been shown to be a more therapeutic alternative to traditional drugs. Vyvanse is approved by the United States Food and Drug Administration (FDA) to treat Attention-Deficit/Hyperactivity Disorder (ADHD), and Binge Eating Disorder. Dextroamphetamine is a serotonin, dopamine, and norepinephrine agonist. The present study investigated the effects of Vyvanse on spatial working memory, body weight, adiposity, activity, and anxiety in rats. Six control and six experimental male rats were placed in individual cages equipped with a running wheel attached to a device that recorded activity. Food and water were provided ad-libitum. The study was divided into three periods: 1) habituation, 2) experimental - in which Vyvanse was given orally to experimental rats, and 3) withdrawal. Control rats received a placebo in periods 2 and 3. Spatial working memory was examined utilizing the methodology of the Morris Water Maze. Animals were evaluated by performance in the maze each day during the experimental and withdrawal periods. Each assessment consisted of two trials. The first was a sample trial in which an escape platform was discovered by trial and error. The second was a test trial in which the platform location was recalled using working memory. Platform placement and start location of the rats were changed every session. It was hypothesized that Vyvanse would effectively enhance spatial working memory in rats and would have a significant influence on body weight and adiposity without side effects on activity level or anxiety. Results supported the hypothesis. Compared to control rats, Vyvanse treated rats had significant improvement in working memory and significantly lowered body weight, as well as significantly decreased mesenteric, renal, and epididymal adiposity. No significant effects on activity level or anxiety were noted in experimental animals. These results support other studies demonstrating that prodrugs can reduce unwanted side effects of the respective active component. Future studies with prodrugs could explore the promising effects of such compounds for treatment of cognitive diseases involving the nervous system.

Disclosures: H.M. Murphy: None. **C.H. Wideman:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.12/HHH17

Topic: H.01. Animal Cognition and Behavior

Title: Exploration of polyfunctional flavonoids based compounds in Alzheimer’s disease: Design, synthesis and biological evaluations

Authors: *M. SINGH[1], O. SILAKARI[2]
[1]Chitkara Col. Of Pharm., Chitkara Univ., Rajpura, India; [2]Dept. of Pharmaceut. Sci. & Drug Res., Punjabi Univ., Patiala, India

Abstract: Polyfunctional compounds comprise a novel class of therapeutic agents for the treatment of multi-factorial diseases like Alzheimer's disease (AD). Following this approach, a new series of flavonoids were designed, synthesized and biologically evaluated against acetylcholinesterase (AChE), advanced glycation end products formation (AGEs) with additional free radical scavenging activity. The *in vitro* studies showed that the majority of synthesized derivatives inhibited acetylcholinesterase (AChE) with IC_{50} values in the nanomolar range. Among them, inhibitors FLV-16 and FLV-32, strongly inhibited AChE, and were more potent than the reference compound donepezil. Moreover, the molecular docking study displayed that most potent compounds simultaneously bind to catalytic active site (CAS) and peripheral anionic site (PAS) of AChE. Besides, these compounds also exhibited greater ability to inhibit advanced glycation end products formation with additional radical scavenging property. Thus, flavonoids might be the promising lead compound as potential poly-functional anti-Alzheimer's agents.

Disclosures: M. Singh: None. **O. Silakari:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.13/HHH18

Topic: H.01. Animal Cognition and Behavior

Support: Career Development Award #BX00167
James S. McDonnell Foundation Grant #220023046

Title: Exercise mediates anesthetic recovery in diabetic and control rats

Authors: *C. SINON[1], A. OTTENSMEYER[2], A. SLONE[3], M. PARDUE[4], P. S. GARCIA[5]
[1]Neurosci., [2]Med., Emory Univ., Atlanta, GA; [3]Medicine, Health, and Society and Child Develop., Vanderbilt Univ., Nashville, TN; [4]Georgia Inst. of Technol., Atlanta, GA; [5]Anesthesiol., Atlanta VA Med. Ctr. / Emory Univ., Decatur, GA

Abstract: Type 2 diabetes mellitus is the most prevalent metabolic disease worldwide. Diabetes is associated with decreases in cortical volume and an increased risk for experiencing cognitive impairments. It has been previously reported that diabetic patients experience impaired cognitive function following cardiac surgery, especially on speed-related tasks. In an animal model of type 1 diabetes, exposure to isoflurane anesthesia without surgery is sufficient to cause memory problems. Exercise is often prescribed for diabetic patients and regular physical activity is

hypothesized to decrease the risk of postoperative cognitive impairments. This study presents the first results of our investigation into the effects of diabetes and of exercise on recovery from isoflurane anesthesia in a type 2 diabetes rat model. Wistar (n = 32) and Goto-Kakizaki (GK) type 2 diabetes (n = 32) rats between 3-4 months old underwent forced treadmill exercise or remained idle on a stationary treadmill for 10 days. Rats then received either a 2-hour exposure to 1.5-2% isoflurane in oxygen at 1L/min or oxygen. At two hours, rats were removed and placed into a recovery chamber. Time to appearance of post-anesthetic milestones were recorded for 30 minutes, after which the rat was moved to a video-monitored rodent cage environment for 1 hour to record post-anesthesia behavior. Pre- and Post-anesthesia Y-maze spatial alternation was recorded to determine cognitive performance on a spatial memory task. At baseline, diabetic rats show a decrease in spontaneous alternation behavior ($p = 0.0291$) and in maze exploration ($p < 0.0001$). Rats receiving ten days of forced treadmill exercise displayed no difference from idle rats in their emergence times from isoflurane general anesthesia (Return of Righting Reflex, $p = 0.9259$), but exercise hastened the appearance of our general recovery marker (Sticky Dot) post anesthesia for both Wistar and GK rats ($p = 0.0079$,). Rats that underwent exercise and isoflurane treatment display a decrease in spatial working memory compared with other experimental groups, as revealed by a significant main effect for anesthetic treatment & activity on a post-anesthesia Y-maze test. At baseline, we found the diabetic rats were less active and showed decreased spatial working memory compared to Wistar rats in the Y-maze. Forced exercise training prior to general anesthesia resulted in hastened recovery from isoflurane regardless of the presence of metabolic syndrome. Despite the lack of an effect of diabetic status on post-anesthesia behavioral outcomes, these results suggest a need for further study of the general interaction between exercise and recovery from anesthesia.

Disclosures: C. Sinon: None. **A. Ottensmeyer:** None. **A. Slone:** None. **M. Pardue:** None. **P.S. Garcia:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.14/HHH19

Topic: H.01. Animal Cognition and Behavior

Support: SEP-PRODEP NPTC-472
VIEP 2018

Title: Effects of the chronic administration of caffeine and pramipexole on recognition memory and nerve growth factor expression in the hippocampus of mice

Authors: *L. MARTINEZ MENDIETA[1], P. HORTA LÓPEZ[2], F. LUNA MORALES[2], V. ALATRISTE BUENO[2], D. I. LIMÓN[2], I. MARTÍNEZ GARCÍA[2]
[2]Pharm., [1]Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: Caffeine is an adenosinergic antagonist, a psychoactive drug widely used around the world. Experiments in animals have been shown that caffeine improves memory, an effect related to modulation of neurotransmitters involved in plasticity at CNS. On the other hand, pramipexole (PPX), a dopaminergic D2/D3 agonist, has described as a drug that enhances the expression of neurotrophins and improves memory in animal models. The aim of the present work was to evaluate the effect of chronic administration of caffeine or PPX on the recognition memory test and its effects on the expression of the nerve growth factor (NGF) and its receptor tyrosine kinase A (TrkA) in the hippocampus. Female, adult, CD1 mice (28-30 g) were housed in groups and different groups were formed with caffeine (0.2 and 0.2 mg/kg i.p.) and saline solution (SSI) as vehicle group daily for 10 days; PPX (0.5 mg/kg i.p.) and SSI as vehicle group daily for 14 days and its vehicle. At the end of pharmacological treatment, the test of recognition of objects was used to evaluate the memory of mice. After animals were sacrificed by an anesthetic administration and each brain was perfused by intracardial administration of paraformaldehyde (4% in PBS, pH=7.4). The immunohistochemistry to NGF and TrkA and Nissel-staining were performed in the hippocampus and expression analysis was done for CA1, CA2, CA3 and dentate gyrus of the hippocampus. Our results showed that caffeine in low doses of 0.1 and 0.2 mg/kg or PPX doesn´t modify the learning and memory tests. In contrast, both treatments of caffeine or PPX caused an increase in the expression of NGF and its receptor TrkA in different areas of the hippocampus in mice. It's highly probably that neurotrophic effects of caffeine and PPX are related to NGF and TrkA expression and its survival pathways, so future studies are needed to understand its beneficial effects.

Disclosures: L. Martinez Mendieta: None. **P. Horta López:** None. **F. Luna Morales:** None. **V. Alatriste Bueno:** None. **D.I. Limón:** None. **I. Martínez García:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.15/HHH20

Topic: H.01. Animal Cognition and Behavior

Title: Standardized extract of ginkgo biloba modulates expression of the brain derived neurotrophic factor (bdnf) in the dorsal hippocampal formation of the rats subjected to the novel object recognition memory

Authors: *B. G. MURATORI[1], C. ZAMBERLAM[2], T. BIUDE[2], B. NOZIMA[2], J. CERUTTI[2], S. CERUTTI[3]

[1]Biol. Sci., Univ. Federal of São Paulo, Sao Paulo, Brazil; [2]Morphology and Genet. Dept., Univ. Federal of São Paulo, São Paulo, Brazil; [3]Morphology and Genetics; Biol. Sci. Dept., Univ. Federal of São Paulo, Sao Paulo, Brazil

Abstract: Data from our group showed that standardized extract of *Ginkgo biloba* (EGb) modulates acquisition and extinction of the conditioned suppression by inducing differential CREB-1, GAP-43 and GFAP gene and protein expression in the dorsal hippocampal formation (DHF). However, it is unclear whether the procognitive effects my be observed in anothers memoris., additional approaches are needed to better understand the effect of EGb on memory, particularly in non-aversive tasks. We investigated the effects of treatment with EGb on acquisition of novel object recognition (NOR) memory in rats. In addition, we investigated the NOR-induced protein expression of the Brain Derived Neurotrophic Factor (BDNF) in the dorsal hippocampal formation (dHF) of control groups (vehicle and Diazepam® (4 $mg.kg^{-1}$) and EGb-treated groups of rats. Adult male Wistar rats from 10-12 weeks old were subjected to handling for five days. A single dose of EGb (0.25, 0.5 and 1.0 $g.kg^{-1}$), Diazepam or vehicle (0,9% salina) was administered prior to the acquisition session (familiarization 1) (day 6), which the animals were exposed to two distinct objects in order to become familiar for 15 min in a wood box (40 x 40 x 40 cm) with a floor demarcated into squares (n = 10/group). Twenty-four hours after (day 7), the animals were subjected to the second familiarization session (familiarization 2), in the same condition described for training 1. On the 8th day, the subjects are allowed to explore two objects (one familiar and one new) to evaluated the NOR memory (T1). Exploration ratio (ER) was calculated to to evaluated differential time spent to explore novel and familiar object. In order to exclude the potential effect of confounding variables, as locomotor and exploratory activity of animals, we also evaluated the number of contact frequency, rearing, ambulation, grooming. The animals were euthanized after completion the test 1 session and the dorsal hippocampal formation (dHF) was extracted to analyze the expression of the BDNF, an important molecules involved on mechanisms underlying **memory** formation by the Western Blot technique. Two-way RM ANOVA revealed a significant interaction between groups and trials ($F_{28,315}$= 2.605; P<0.0001).The mean ER showed that EGb-treated groups (250 $mg.Kg^{-1}$; ER=0.70; P=0.0011; 500 $mg.Kg^{-1}$, ER=0.66; P=0.0084; and 1000 $mg.Kg^{-1}$, ER=0.86; P<0.0001) take more time explore new object when compared with vehicle group (TE=0.42). Furthermore, EGb increased, in a dose-dependent manner, the BDNF levels in the dHF. Our data show that EGb modulates non-aversive memory acquisition, which was associated with increased BDNF expression in DHF.

Disclosures: B.G. Muratori: None. **C. Zamberlam:** None. **T. Biude:** None. **B. Nozima:** None. **J. Cerutti:** None. **S. Cerutti:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.16/HHH21

Topic: H.01. Animal Cognition and Behavior

Title: Subchronic treatment with Morin improves memory in healthy mice

Authors: *H. MARTINEZ-CORIA[1,2], N. SERRANO GARCIA[2], G. S. LOPEZ-CHAVEZ[2], A. Y. GONZALEZ-MUÑIZ[2], H. E. LOPEZ-VALDES[1], M. OROZCO-IBARRA[2], M. A. TORRES-RAMOS[2]
[1]Univ. Nacional Autonoma de Mexico, Mexico City, Mexico; [2]Inst. Nacional de Neurología y Neurocirugía, Mexico City, Mexico

Abstract: Introduction: Cognitive improvement has been linked to the consumption of various polyphenols of natural origin. Morin is a polyphenol present in various fruits such as figs and blackberries, has antioxidant, neuroprotective and anti-inflammatory activity, among others. The brain regions involved in memory are the hippocampus and the entorhinal cortex, responsible for memory consolidation and one of the first brain regions to be affected in Alzheimer's disease.
Objective: To characterize the effect of morin on recognition memory in healthy adult mice and their possible molecular mechanism.
Material and Methods: 60 healthy adult mice (25-30 g, C57BL / 6) were divided into groups of 10 animals: control (saline solution), vehicle (DMSO) and those treated with morin. Morin was administered i.p. In different doses (1, 2.5, 5 and 10 mg / kg / 24 h for 10 days). The new object recognition memory test was performed at 10 days of treatment. The brains of the mice were processed for histological characterization and protein expression by immunohistochemistry analysis.
Results: The IR index obtained in the different groups was (% ± SEM): Control = 60 ± 1.8, Vehicle = 64 ± 3.0, 1 mg / kg = 79 ± 4.15, 2.5 mg / kg = 72.31 ± 4.58, 5 mg / kg = 69.95 ± 4.05, 10 mg / kg = 64.39 ± 5.61. Significant IR was observed in mice treated with 1 mg / kg of morin relative to control and vehicle ($p < 0.001$ and $p < 0.01$ respectively, ANOVA followed by Tukey's post hoc test). The behavioral effect correlates with increased expression of the IL-4, GFAP and pro-BDNF proteins.
Discussion and Conclusions: Morin, in low concentrations, improves memory recognition of new object in healthy adult mice. We suggest that the molecular mechanism involved is due to the production of BDNF via the activation of astrocytes produced by the increase of IL-4. Activation of astrocytes by IL-4 and IL-13 has been reported to favor the production of BDNF involved in improved memory and increased expression of proteins involved in the synapse.

Disclosures: H. Martinez-Coria: None. **N. Serrano Garcia:** None. **G.S. Lopez-Chavez:** None. **A.Y. Gonzalez-Muñiz:** None. **H.E. Lopez-Valdes:** None. **M. Orozco-Ibarra:** None. **M.A. Torres-Ramos:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.17/HHH22

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA06634

Title: Cognitive consequences of opioid analgesics on nonhuman primate memory

Authors: *C. JOHNSON[1], B. M. ROEDER[2], J. B. DAUNAIS[5], J. R. STAPLETON-KOTLOSKI[6], J. A. ROWLAND[7], E. E. ROGERS[7], C. T. WHITLOW[7], L. J. PORRINO[3], S. A. DEADWYLER[4], R. E. HAMPSON[4]
[1]Wake Forest Sch. of Med., Winston-Salem, NC; [2]Neurosci., [3]Physiol. & Pharmacol., [4]Wake Forest Sch. of Med., Winston Salem, NC; [5]Dept Physiol & Pharmacol, [6]Neurol., [7]Wake Forest Univ. Sch. of Med., Winston Salem, NC

Abstract: The use and abuse of opioid analgesics has become a major problem for public health. In addition to the abuse potential, there is growing concern for both acute and long-term cognitive consequences for use of opioid pain relievers. Prior findings from this Program have demonstrated that cognitive processing by nonhuman primates (NHPs) in a delayed match to sample (DMS) memory task is altered via hippocampal and prefrontal cortical disruption by drugs of abuse (Hampson et al., Psychopharmacology, 2011; 213:105-118), sleep deprivation (Porrino et al., PLoS Biology, 2005; 3:e299) and whole-brain irradiation (Robbins et al., Radiat Res., 2011; 175:519–525). We therefore initiated a pilot study to determine cognitive effects of acute does of opioid agonists and antagonists in support of efforts to develop effective addiction therapies and alternatives to opioid analgesics.
Four nonhuman primates (NHPs) were tested for acute effects of full and partial opioid agonists and antagonists to compare effects on performance of a complex memory task. NHPs (macaca mulatta) were trained in a rule based spatial vs. object delayed match-to-sample (DMS; Hampson et al., 2013) task with 2-7 images placed on eight symmetric locations on the screen with variable delay epochs of 1-60s. The following opioids were tested: Naltrexone (antagonist) 0.1 and 0.3 mg/kg i.m., Oxycodone (agonist) 0.3 mg/kg i.m., Buprenorphine (partial agonist) 0.06 mg/kg i.m., Methadone (agonist) 0.5 mg/kg i.m. Naltrexone 0.01 mg/kg IV was kept on hand as a rescue dose in case of respiratory depression, anesthesia or distress. NHPs received drug 30 minutes before DMS testing twice per week, with a minimum of two days between drug administration.

Results showed that low dose naltrexone (0.1 mg/kg i.m.) had no effect on performance of the DMS task (and was actually facilitatory in one NHP); however the high dose (0.3 mg/kg i.m.) as well as oxycodone and buprenorphine suppressed DMS performance by as much as 15%. Methodone was still in testing at the time of submission. Thus the use of alternate opioid agonists/antagonists in the course of addiction treatment still risks cognitive impairment. Results will be further discussed in terms of magnetoenchephalographic (MEG) and functional magnetic resonance (fMRI) imaging or resting state brain activity in the same NHPs to determine neural substrates affected by opiates, as well as analysis of proposed countermeasures for opiate analgesic addiction and their consequences on cognition and memory.

Disclosures: C. Johnson: None. **B.M. Roeder:** None. **J.B. Daunais:** None. **J.R. Stapleton-Kotloski:** None. **J.A. Rowland:** None. **E.E. Rogers:** None. **C.T. Whitlow:** None. **L.J. Porrino:** None. **S.A. Deadwyler:** None. **R.E. Hampson:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.18/HHH23

Topic: H.01. Animal Cognition and Behavior

Support: SoMoPro II Programme (Project N° 3SGA5789)

Title: Behavioral and molecular effects of peripubertal cannabidiol treatment on perinatal delta-9-tetrahydrocannabinol exposed rats

Authors: *V. MICALE[1,2], T. STARK[3], G. GIURDANELLA[2], M. KUCHAř[1], C. D'ADDARIO[4], F. DRAGO[5], R. MECHOULAM[6], S. SALOMONE[5], A. SULCOVA[3]
[1]Natl. Inst. Mental Hlth., Klecany, Czech Republic; [2]Dept of Biomed. and Biotechnological Sci., Catania, Italy; [3]Masaryk Univ., Brno, Czech Republic; [4]Univ. of Teramo, Teramo, Italy; [5]Dept of Biomed. and Biotechnological Sciences,, Catania, Italy; [6]Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Epidemiological and clinical studies suggest that a neurodevelopmental dysfunction could be one of the main exploratory hypotheses of schizophrenia (SCZ), which symptoms lead to severe personal and social dysfunctions. A variety of animal and human studies found a dysregulation of the endocannabinoid system (both in term of cannabinoid receptors CB1 or CB2 and endocannabinoid ligands anandamide or 2-arachidonoylglycerol) in psychosis; thus, the pharmacological exploitation of the endocannabinoid system could be a novel approach for treating SCZ. In the present study, we aimed to investigate 1) the potential effects of perinatal administration of delta-9-tetrahydrocannabinol (Δ^9-THC), the main psychotropic compound of *Cannabis sativa* on neurophenotypic presentations using a set of behavioral test battery, and 2) if

the pharmacological modulation of the endocannabinoid signaling could reverse the schizophrenia-like phenotype. At adulthood, Δ^9-THC -exposed rats engaged in less social interaction as well as they shown cognitive impairment, which were reversed by the chronic treatment with the non-psychotropic phytocannabinoid cannabidiol (CBD). At molecular level the altered cannabinoid CB1 expression in the prefrontal cortex was also reversed by CBD treatment. These results suggest that pharmacological modulation of the endocannabinoid tone could be a novel potential therapeutic target for the treatment of schizo-affective disorders.

Disclosures: V. Micale: None. **T. Stark:** None. **G. Giurdanella:** None. **M. Kuchař:** None. **C. D'Addario:** None. **F. Drago:** None. **R. Mechoulam:** None. **S. Salomone:** None. **A. Sulcova:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.19/HHH24

Topic: H.01. Animal Cognition and Behavior

Support: PAPIIT IN215816
CONACYT 453816

Title: Two rounds of transcriptional regulation in the insular cortex are necessary for conditioned taste aversión storage

Authors: *L. A. RODRÍGUEZ-BLANCO[1], A. RIVERA-OLVERA[1], M. L. ESCOBAR[2]
[1]Facultad de Psicologia, UNAM, Mexico City, Mexico; [2]UNAM, Fac Psicologia, Mexico City, Mexico

Abstract: Nowadays it is widely accepted that long-term memory (LTM) establishment requires synthesis of new proteins, even many hours after memory acquisition. Some studies have shown the existence of at least two different time windows for the amnesic effect of protein synthesis inhibitors. In this regard, we have previously reported that protein synthesis inhibition 7 hours after acquisition in the insular cortex (IC) prevents the consolidation of conditioned taste aversion (CTA), a well-established learning and memory paradigm in which an animal associates a novel taste with nausea. In spite of this, little is known about the requirement of new mRNA during storage of CTA-LTM. Behavioral studies have emphasized the importance of a single time window sensitive to inhibitors of mRNA synthesis at or around the time of training. On the other hand, regulation of transcription through epigenetic mechanisms has been shown to occur in response to new experiences which result in gene expression changes that are necessary for LTM storage. Accordingly, it has been demonstrated that transcription regulation via histone acetylation is essential for memory establishment. The aim of the present study was to evaluate

the effect of the inhibition of transcription as well as deacetylation of histones in the IC at two temporal windows on the consolidation of CTA, through an intracortical microinfusion of 5,6-dichloro-1-beta-D ribofuranosyl-benzimidazole (DRB) or MS-275, respectively. Thus, animals received a microinfusion of DRB or MS-275 in the IC either immediately or 7 hours after CTA acquisition. Our results show that transcription inhibition impairs CTA memory consolidation, whereas histone deacetylation inhibition strengths this memory immediately and 7 hours after the acquisition session. These findings reveal that CTA memory requires at least two rounds of transcriptional modulation events in the IC in order to consolidate this memory trace.

Disclosures: L.A. Rodríguez-Blanco: None. **A. Rivera-olvera:** None. **M.L. Escobar:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.20/HHH25

Topic: H.01. Animal Cognition and Behavior

Support: CONACYT 250870
CONACYT FOIINS 474
PAPIIT IN208616

Title: Effect of the inhibition of palmitoylation on the formation and maintenance of spatial memory

Authors: *O. G. URREGO MORALES[1], I. DELINT-RAMÍREZ[2], F. BERMUDEZ-RATTONI[3]
[1]Univ. Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico; [2]Dept. of Psychiatry, Univ. of Texas Southwestern Med. Ctr., Austin, TX; [3]UNAM, Mexico City DF 04510, Mexico

Abstract: Protein palmitoylation (addition of lipid palmitate) is a post-translational modification that modifies the hydrophobicity of proteins. This process allows the interaction of proteins with the lipids of the cell membrane and the subcellular membranes, regulating the location and function of these proteins. In the nervous system, palmitoylation regulates vesicular trafficking and the localization of neurotransmitter receptor proteins in processes of synaptic plasticity. The genetic and pharmacological approaches in murine models have reported the participation of palmitoylation in spatial memory processes. However, these approaches have not evaluated the effects of palmitoylation during the different phases of spatial memory; that is, acquisition, consolidation and retrieval. Therefore, in this work, we studied the participation of palmitoylation during the three phases of memory to understand a possible regulatory mechanism of the proteins involved in memory processes. For this, we evaluated the effect of the inhibition of the palmitoyl acyltransferase enzymes in the dorsal hippocampus with the

irreversible 2-bromopalmitate inhibitor. The drug was administered to different groups of animals during the three phases of memory in two different behavioral models of spatial memory that depend on hippocampal activity. The results showed that the inhibition of palmitoylation affected the acquisition and consolidation, but not spatial memory retrieval. In addition, it was observed that the expression of glutamatergic receptors NMDA and AMPA in the hippocampus increases after learning. The expression of the AMPA receptor was modified when the palmitoyl acyltransferase enzymes were inhibited, but the NMDA receptor remained unchanged. In conclusion, palmitoylation of proteins mediated by palmitoyl acyltransferase enzymes participates in the formation and maintenance of spatial memory throughout AMPA receptor trafficking.

Disclosures: O.G. Urrego Morales: None. **I. Delint-Ramírez:** None. **F. Bermudez-Rattoni:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.21/HHH26

Topic: H.01. Animal Cognition and Behavior

Support: R01 AA019894
P50 AA22534
GM060201

Title: Prenatal alcohol-induced deficits in trace fear conditioning and Morris water maze place learning are ameliorated by the histamine H_3 receptor inverse agonist SAR152954

Authors: *J. L. WAGNER[1,2], S. D. DAVIES, 87131[2], A. H. MOEZZI[2], K. S. LUJAN[2], E. J. RAPPAPORT[2], D. A. HAMILTON, 87131[2,3], D. SAVAGE, II[2]
[1]Albuquerque, NM; [2]Neurosciences, [3]Psychology, Univ. of New Mexcio, Albuquerque, NM

Abstract: Hippocampal-sensitive behaviors, such as contextual fear conditioning and spatial navigation, are among the learning tasks most affected by prenatal alcohol exposure (PAE). These tasks could serve as behavioral screening tools for novel agents with efficacy in treating learning disabilities associated with Fetal Alcohol Spectrum Disorder (FASD). We have reported that a single treatment with the histamine H3 receptor inverse agonist ABT-239, administered at the onset of training in either one trial of delay contextual fear conditioning or water maze place training, reverses PAE-induced deficits in the retention of learning. Here, we investigated the ability of a second H3 receptor inverse agonist namely, SAR152954, to affect PAE-induced deficits in fear-conditioned learning and on spatial learning and memory. Moderate PAE offspring were generated as described by Savage et al., (2010). Offspring from 38 separate Long

Evans rat dams were weaned at PD24 and group-housed until six months of age. On the first day of training, offspring from each prenatal treatment group were given a single injection of either 0.1 mg/kg SAR152954 or vehicle 30 minutes prior to the first training trial. Female offspring were then subjected to fear conditioning, in which they are given two trials separated by a 90-second inter-trial interval. Each trial consisted of a 5-second 90 dB tone conditioned stimulus (CS), followed by a 60-second trace interval that co-terminated with a 2-second 1 mA foot-shock unconditioned stimulus (US). One day later, the rats were exposed to a single CS exposure to test for retention of the CS-US association. After a single injection of SAR1521954, male offspring were given 12 Morris water maze place-training trials in series with an inter-trial interval of 5-10 minutes. One week later, the rats were tested for retention of the place location. There were no main or interactive effects of prenatal group or drug treatment on acquisition during training in either trace fear conditioning or Morris Water Maze place acquisition. However, in both behavioral tasks, a two-way repeated measures ANOVA revealed a prenatal group by drug interaction. Saline-treated PAE rats performed significantly worse than either control group during test trials. Performance by SAR152954-treated PAE rats was significantly better than vehicle-treated PAE rats and not different than control groups. These results indicate that SAR152954, another H3 receptor inverse agonist, reverses PAE-induced deficits in hippocampal-sensitive learning tasks and that agents with this mechanism of action warrant consideration as novel agents in treating learning deficits associated with FASD.

Disclosures: J.L. Wagner: None. **S.D. Davies:** None. **A.H. Moezzi:** None. **K.S. Lujan:** None. **E.J. Rappaport:** None. **D.A. Hamilton:** None. **D. Savage:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.22/HHH27

Topic: H.01. Animal Cognition and Behavior

Support: the National Natural Science Foundation of China Grant Nos. 81600983
the National Natural Science Foundation of China Grant Nos. 31771178
the National Natural Science Foundation of China Grant Nos. 81600991
the Start-up Fund from Wenzhou Medical University Nos. 89211010
the Start-up Fund from Wenzhou Medical University Nos. 89212012
the Zhejiang Provincial Special Funds No. 604161241
the Wenzhou Science and Technology Program Nos. 2016Y0725

Title: Pharmacological blockade of adenosine A_{2A}but not A_1 receptors enhances goal-directed valuation in satiety-based instrumental behavior

Authors: *J.-F. CHEN[1,2], Y. LI[3], Y. HE[2], X. PAN[2], Y. RUAN[2], L. HUANG[2], C. HE[2], Z. WANG[3], X. ZHANG[3]
[1]Neurol., Wenzhou Med. Univ., Zhejiang, China; [2]Sch. of Optometry and Ophthalmology and Eye Hospital, The Inst. of Mol. Medicine, Wenzhou Med. Univ., Wenzhou, China; [3]Dept. of Neurology, The 2nd Affiliated Hosp. and Yuying Children's Hosp. of Wenzhou Med. Univ., Wenzhou, China

Abstract: The balance and smooth shift between flexible, goal-directed behaviors and repetitive, habitual actions are critical to optimal performance of behavioral tasks. The striatum plays an essential role in control of goal-directed versus habitual behaviors through a rich interplay of the numerous neurotransmitters and neuromodulators to modify the input, processing and output functions of the striatum. The adenosine receptors (namely A_{2A}R and A_1R), with their high expression pattern in the striatum and abilities to interact and integrate dopamine, glutamate and cannabinoid signals in the striatum, may represent novel therapeutic targets for modulating instrumental behavior. In this study, we examined the effects of pharmacological blockade of the A_{2A}Rs and A_1Rs on goal-directed versus habitual behaviors in different information processing phases of instrumental learning using a satiety-based instrumental behavior procedure. We found that A_{2A}R antagonist acts at the coding, consolidation and expression phases of instrumental learning to modulate animals' sensitivity to goal-directed valuation without modifying action-outcome contingency. However, Pharmacological blockade and genetic knockout of A_1Rs did not affect acquisition or sensitivity to goal-valuation of instrumental behavior. These findings provide pharmacological evidence for a potential therapeutic strategy to control abnormal instrumental behaviors associated with drug addiction and obsessive-compulsive disorder by targeting the A_{2A}R.

Disclosures: J. Chen: None. **Y. Li:** None. **Y. He:** None. **X. Pan:** None. **Y. Ruan:** None. **L. Huang:** None. **C. He:** None. **Z. Wang:** None. **X. Zhang:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.23/HHH28

Topic: H.01. Animal Cognition and Behavior

Title: Antagonism of muscarinic, but not estrogen receptors, impairs divided attention in male rats

Authors: *N. PISTORY, P. R. NICKLAS, M. L. GROFT, K. ZIMMER, D. E. MOSURA, W. R. HAWLEY, P. J. MCLAUGHLIN
Dept. of Psychology, Edinboro Univ. of Pennsylvania, Edinboro, PA

Abstract: GPR30 is a central, membrane-bound estrogen receptor that is expressed in basal forebrain cholinergic cells, and which regulates cholinergic outflow in hippocampus. The receptor plays a role in spatial working memory that may be mediated by muscarinic receptors. Regulation of other cognitive processes has been speculated, but not demonstrated. Divided attention (DA) is an understudied cognitive domain that may be increasing in health relevance with added distractors in daily experience, and may also be vulnerable in dementia. We developed an operant, crossmodal model of DA in male rats which featured an auditory sustained attention (SA) component, with an unpredictable, low reinforcement-rate visual distractor task using preferred reinforcers. Experiment 1 compared effects of the muscarinic antagonist scopolamine on both SA and DA (i.e., SA with a distractor) tasks. The DA task was found to be more challenging, as evidenced by lower stimulus sensitivity (d'). Scopolamine impaired performance similarly on both tasks, contrary to expectation. However, a floor effect may have been present, due to low baseline performance of the DA task. After the first experiment, auditory signal durations were increased in order to reduce attentional load. Doing so produced higher baseline performance, similar to the SA task. In Experiment 2, the GPR30 antagonist G15 (0.5 and 1.0 mg/kg) was given subcutaneously, both alone and prior to administration of a dose of scopolamine (0.05 mg/kg) that was subeffective in Experiment 1. It was hypothesized that G15 would impair DA alone, or potentiate the effect of low-dose scopolamine. In Experiment 2, only DA was assessed, using the version with longer stimulus durations. G15 was ineffective, either alone or prior to scopolamine. However, scopolamine impaired DA, in line with the proposed floor effect in Experiment 1. The inability of G15 to alter effects of scopolamine on DA may indicate a dissociation of the role of GPR30 in DA, compared with spatial working memory, although longer-term administration may also be required. There may also be a lack of endogenous tone of estrogen in cholinergic regulation. In any event, these results suggest a limited role of GPR30 blockade in attention in the presence of increased distraction.

Disclosures: N. Pistory: None. **P.R. Nicklas:** None. **M.L. Groft:** None. **K. Zimmer:** None. **D.E. Mosura:** None. **W.R. Hawley:** None. **P.J. McLaughlin:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.24/HHH29

Topic: H.01. Animal Cognition and Behavior

Support: NIMH MH104158-05

Title: Potentiation of muscarinic acetylcholine receptor 4 (m_4) as compensation for transcription factor 4(tcf4) deficiency

Authors: *A. MOORE[1], A. J. WU[2], J. D. WEISS[1], L. CHEN[2], R. G. GOGLIOTTI[1], C. M. NISWENDER[1], J. D. SWEATT[1]
[1]Pharmacol., [2]Col. of Arts and Sci., Vanderbilt Univ., Nashville, TN

Abstract: Transcription Factor 4 (TCF4) regulates several important neuronal processes such as DNA methylation, long-term potentiation and memory formation. Mutations in the gene encoding TCF4 cause the neurodevelopmental disorder, Pitt Hopkins Syndrome (PTHS) and single nucleotide polymorphisms (SNPs) of TCF4 have been associated with schizophrenia. PTHS is characterized by severe intellectual disability, autism-associated behaviors, motor incoordination, breathing abnormalities and impaired gastrointestinal motility. There are currently no available treatments for PTHS patients. The Sweatt laboratory has characterized a genetically engineered mouse model of PTHS that shows deficiencies in learning and memory. Further characterization of this line revealed a significantly increased rate of breathing that may be comparable to tachypnea observed in PTHS patients. RNA sequencing studies of wild type (WT) and *Tcf4*$^{+/-}$ mouse hippocampal tissue have shown a significant increase in *Chrm4* transcript levels in *Tcf4*$^{+/-}$ mice, the gene that encodes the M_4 muscarinic acetylcholine receptor which suggests TCF4 may regulate *Chrm4* transcription. Recent work from the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD) has shown that potentiation of M_4 receptor signaling yields cognitive-enhancing effects in a mouse model of psychosis, positioning this receptor as a novel therapeutic target for schizophrenia. We report here that a positive allosteric modulator of the M_4 receptor exhibits cognition-enhancing effects in Tcf4-haploinsufficient mice. Excitingly, in addition to our results in a rodent model of Tcf4 deficiency, M_4 receptor potentiation has also shown efficacy in models of other neurodevelopmental disorders, such as Rett syndrome and Fragile X syndrome, where it has recently been shown that enhancement of M_4 receptor signaling can normalize cognitive phenotypes. These data suggest that regulation of M_4 signaling plays a role in compensating for cognitive dysfunction in multiple neurodevelopmental disorders and the current study aims to validate the M_4 receptor as a novel target for PTHS.
We thank the Pitt Hopkins Research Foundation for funding through the Sarah Huffman Young Investigator Award.

Disclosures: A. Moore: None. **A.J. Wu:** None. **J.D. Weiss:** None. **L. Chen:** None. **R.G. Gogliotti:** A. Employment/Salary (full or part-time):; Vanderbilt Center for Neuroscience Drug Discovery. **C.M. Niswender:** A. Employment/Salary (full or part-time):; Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt Kennedy Center. **J.D. Sweatt:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.25/HHH30

Topic: H.01. Animal Cognition and Behavior

Support: PhRMA Foundation Postdoctoral Fellowship in Pharmacology/Toxicology
NIMH P30 MH075673
NIMH PO1MH105280
Johns Hopkins PREP R25GM109441

Title: Pharmacokinetics and safety of intranasal versus subcutaneous insulin for brain delivery in the mouse

Authors: *M. NEDELCOVYCH[1], L. LOVELL[4], A. GADIANO[2], Y. WU[4], A. MANNING[4], A. G. THOMAS[5], S. S. KHUDER[3], S. YOO[3], J. XU[3], J. MCARTHUR[3], N. J. HAUGHEY[6], D. VOLSKY[7], R. RAIS[4], B. S. SLUSHER[4]
[1]Dept. of Neurol., [2]Johns Hopkins Drug Discovery, [3]Johns Hopkins Univ., Baltimore, MD; [4]Johns Hopkins Drug Discovery, Baltimore, MD; [5]Johns Hopkins Drug Discovery, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [6]Neurol., Johns Hopkins, Baltimore, MD; [7]Infectious Diseases-Medicine, Annenberg Bldg., 21-42, New York, NY

Abstract: Insulin delivery to the brain has recently been identified as a potential therapeutic target for cognitive disorders associated with abnormal brain energy metabolism. Although insulin is transported across the blood-brain barrier, peripheral routes of administration are problematic due to systemic effects of insulin on blood glucose. Intranasal (IN) administration is being investigated as an alternative route. We conducted a direct comparison of subcutaneous (SC) and IN insulin, assessing plasma and brain pharmacokinetics and blood glucose levels in the mouse. SC insulin (2.4 IU) achieved therapeutically relevant concentrations in the brain but dramatically increased plasma insulin, resulting in severe hypoglycemia and in some cases death. IN administration of the same dose resulted in similar insulin levels in the brain but substantially lower plasma concentrations. IN dosing had no significant effect on blood glucose. When administered daily for 9 days, IN insulin increased brain glucose and energy metabolite concentrations without causing overt adverse effects. We next assessed whether insulin delivered via the IN route could achieve dose linearity in the brain, and conducted a preliminary assessment of its therapeutic index by neurohistopathology. Together, these findings suggest that IN insulin may be a safe therapeutic option for cognitively impaired patients.

Disclosures: M. Nedelcovych: None. **L. Lovell:** None. **A. Gadiano:** None. **Y. Wu:** None. **A. Manning:** None. **A.G. Thomas:** None. **S.S. Khuder:** None. **S. Yoo:** None. **J. Xu:** None. **J. McArthur:** None. **N.J. Haughey:** None. **D. Volsky:** None. **R. Rais:** None. **B.S. Slusher:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.26/HHH31

Topic: H.01. Animal Cognition and Behavior

Title: A central nervous system-penetrant soluble guanylate cyclase stimulator reduced spine density loss in aged rats and mice

Authors: *S. CORREIA[1], J. E. JONES[1], C. REX[2], G. LIU[1], A. CARVALHO[1], P. GERMANO[1], R. R. IYENGAR[1], C. J. WINROW[1], M. G. CURRIE[1], J. R. HADCOCK[1]
[1]Ironwood Pharmaceuticals, Cambridge, MA; [2]Dept of Neurobio., Afraxis Inc., San Diego, CA

Abstract: Soluble guanylate cyclase (sGC) is a signaling enzyme expressed in many cell types in the body including the central nervous system (CNS), and its activity results in the production of cyclic guanosine-3′,5′-monophosphate (cGMP) from guanosine-5′-triphosphate (GTP). We evaluated the effects of IWP-247, a CNS-penetrant sGC stimulator, on spine density in pyramidal neurons of the CA1 hippocampal area and layer 3 medial prefrontal cortex (L3 mPFC) of aged rats and mice. During normal aging, the number of spines is reduced in many brain areas, and spine loss correlates with decreased synaptic function. Spine loss is exacerbated in neurodegenerative disorders such as Alzheimer's Disease and is thought to contribute to dementia symptoms. In the first study, 16-month-old male C57BL6 mice were treated for 4 months with either 1 mg/kg IWP-247 or vehicle in rodent chow. Three-month old mice were also treated with vehicle rodent chow for 4 months. Brains were collected, labeled with DiI, and hippocampal CA1 and L3 mPFC pyramidal neurons were imaged using Airyscan super-resolution microscopy. 3D images were analyzed for spine density and morphology by analysts blinded to experimental conditions. The density of mushroom-type spines in CA1 hippocampal neurons of aged mice treated with vehicle chow was lower than in young mice. The density of mushroom spines in CA1 neurons of aged mice treated with IWP-247 was greater than in aged vehicle-treated mice and similar as in young mice. There was no difference in spine density of L3 mPFC pyramidal neurons between any groups. In the second study, 22- to 24-month-old rats were treated with 0.3 or 1 mg/kg IWP-247, or vehicle in chow for 1 month. Two- to three-month old rats were also treated with vehicle rodent chow for 1 month. Brains from the rats in the 4 groups were collected and processed as described above. The density of total spines in L3 mPFC neurons in aged rats treated with 1 mg/kg IWP-247 was comparable to the young rats, and greater than in aged vehicle rats. Overall these results suggest that sGC stimulation may provide neuroprotective effects and improve synaptic function by reducing spine density loss in neurodegenerative diseases.

Disclosures: S. Correia: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **J.E. Jones:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **C. Rex:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Afraxis. **G. Liu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **A. Carvalho:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood pharmaceuticals. **P. Germano:** E.

Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **R.R. Iyengar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **C.J. Winrow:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **M.G. Currie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **J.R. Hadcock:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.27/HHH32

Topic: H.01. Animal Cognition and Behavior

Title: The brain penetrant soluble guanylate cyclase stimulator IWP-247 improved thigmotaxis and increased hippocampal N-acetylaspartate (NAA) concentrations in aged rats

Authors: *J. E. JONES[1], C. J. WINROW[1], S. S. CORREIA[1], S. JACOBSON[1], R. HODGSON[2], J. PUOLIVALI[2], K. LEHTIMÄKI[2], A. CARVALHOA[1], P. GERMANO[1], J. V. TOBIN[1], K. TANG[1], R. R. IYENGARA[1], M. G. CURRIE[1], J. R. HADCOCK[1]
[1]Ironwood Pharmaceuticals, Cambridge, MA; [2]Charles River Discovery, Kuopio, Finland

Abstract: The number of Americans 65 or older is projected to more than double in the next 40 years to 88.5 million by 2050. Even in individuals without dementia, many will experience age-associated memory impairment as part of the normal aging process which is associated with reduced brain metabolites such as N-acetylaspartate (NAA) and N-acetyl aspartyl glutamate (NAAG). Soluble guanylate cyclase (sGC) stimulators are small molecules that potentiate the nitric oxide (NO)-sGC-3',5'-cyclic Guanosine Monophosphate (cGMP) signaling pathway, causing increased cGMP production, which modulates physiological mechanisms such as vasodilation, fibrosis, and inflammation. This study investigated the effects of IWP-247, a CNS-penetrant sGC stimulator, on cognitive deficits and hippocampal brain metabolites caused by the normal progression of aging in healthy 21-month-old male Wistar rats.
Rats received daily oral doses of IWP-247 or vehicle and were tested in the Morris water maze (MWM). Aged rats received vehicle (n=17) or IWP-247 (1 mg/kg, n=18, or 10 mg/kg, n=20); and young rats (2-3 months old) received vehicle (n=20). Daily dosing occurred 30 min before MWM training or testing. MWM began following the first dose on day 1 with visible platform training, followed by hidden platform training on days 2-9, and a probe trial on day 10. There

were no significant differences in visible platform training between groups including swimming speed. During hidden platform training, all groups of aged rats had significantly higher thigmotaxis (measure of strategy) values than young rats. Both groups of aged IWP-247-treated rats had significant improvements in thigmotaxis compared to aged vehicle-treated rats and thigmotaxis values equivalent to young rats by day 4. By day 9, all aged rats performed like the young rats, suggesting that aged healthy rats have a minor impairment in learning and when given enough training can perform equally to young rats. IWP-247 appeared to accelerate the learning process in the MWM paradigm. Following the MWM study, rats continued on their prior dosing regimens for 20 more days. On day 30, one hr after oral administration of vehicle or IWP-247, hippocampal magnetic resonance spectroscopy (MRS) was performed and brain metabolites analyzed. Aged vehicle-treated rats had significantly lower levels of NAA+NAAG compared to young vehicle-treated rats. Levels of NAA+NAAG were similar in aged rats treated with either dose of IWP-247 and young vehicle-treated rats. In conclusion, treatment with IWP-247 had a beneficial effect on cognitive performance and restored important hippocampal brain metabolites in 21-month-old male Wistar rats.

Disclosures: **J.E. Jones:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **C.J. Winrow:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **S.S. Correia:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **S. Jacobson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **R. Hodgson:** None. **J. Puolivali:** None. **K. Lehtimäki:** None. **A. Carvalhoa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **P. Germano:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **J.V. Tobin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **K. Tang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **R.R. Iyengara:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **M.G. Currie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **J.R. Hadcock:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.28/HHH33

Topic: H.01. Animal Cognition and Behavior

Support: CAPES

Title: Synaptic consolidation as a temporally variable process: Uncovering theparameters modulating its time-course

Authors: *M. A. CASAGRANDE[1], J. HAUBRICH[2], L. K. PEDRAZA[1], B. POPIK[1], J. A. QUILLFELDT[1], L. D. ALVARES[1]
[1]Univ. Federal do Rio Grande do Sul, Porto Alegre, Brazil; [2]McGill Univ., Montreal, QC, Canada

Abstract: Memories are not instantly created in the brain, requiring a gradual stabilization process called consolidation to be stored and persist in a long-lasting manner. However, little is known whether this time-dependent process is dynamic or static, and the factors that might modulate it. Here, we hypothesized that the time-course of consolidation could be affected by specific learning parameters, changing the time window where memory is susceptible to retroactive interference. In the rodent contextual fear conditioning paradigm, we compared weak and strong training protocols and found that in the latter memory is susceptible to post-training hippocampal inactivation for a shorter period of time. The accelerated consolidation process triggered by the strong training was mediated by glucocorticoids, since this effect was blocked by pre-training administration of metyrapone. In addition, we found that pre-exposure to the training context also accelerates fear memory consolidation. Hence, our results demonstrate that the time window in which memory is susceptible to post-training interferences varies depending on fear conditioning intensity and contextual familiarity. We propose that the time-course of memory consolidation is dynamic, being directly affected by attributes of the learning experiences.

Disclosures: J. Haubrich: None. **L.K. Pedraza:** None. **B. Popik:** None. **J.A. Quillfeldt:** None. **L.D. Alvares:** None.

Poster

692. Learning and Memory: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 692.29/HHH34

Topic: H.01. Animal Cognition and Behavior

Title: A central nervous system-penetrant soluble guanylate cyclase stimulator increases cerebral blood flow and modulates fMRI-BOLD responses in rodents

Authors: *C. J. WINROW[1], J. E. JONES[1], P. GERMANO[1], S. JACOBSON[1], S. S. CORREIA[1], K. W. TANG[2], J. TOBIN[1], R. R. IYENGAR[1], P. P. KULKARNI[3], C. F. FERRIS[4], M. CURRIE[1], J. R. HADCOCK[1]
[1]Neurosci., Ironwood Pharmaceuticals, Cambridge, MA; [2]Axial Biotherapeutics, Boston, MA; [3]Psychology, Northeastern Univ. Dept. of Psychology, Boston, MA; [4]Psychology, Northeastern University, Ctr. for Translational NeuroImaging, Boston, MA

Abstract: Disrupted cerebral blood flow (CBF), diminished endothelial function, and dysregulation of the neurovascular unit are key components of several neurological diseases, and are commonly observed in many dementias. Nitric oxide (NO) signals through soluble guanylate cyclase (sGC) to produce 3',5'-cyclic guanosine monophosphate (cGMP) from guanosine-5'-triphosphate (GTP), resulting in the modulation of a variety of physiological processes including blood flow, inflammation, and endothelial and neuronal function. NO-sGC-cGMP signaling is also impaired across a variety of neurological diseases including Alzheimer's disease and vascular dementia. Given its critical role in modulating NO signaling, sGC has emerged as a therapeutic target for diseases in which NO-sGC-cGMP signaling is impaired. IWP-247 is an orally bioavailable, central nervous system (CNS)-penetrant, small-molecule sGC stimulator that increases cGMP levels throughout the brain in animal models. We evaluated the effects of IWP-247 on CBF using cranial laser doppler and fMRI-BOLD in rodent studies. Regional CBF was measured in anesthetized male rats. Following baseline recording, intravenous administration of the nitric oxide synthetase inhibitor N(ω)-nitro-L-arginine methyl ester (L-NAME) was delivered to induce a 25% reduction in CBF. Following the reduction in CBF, subcutaneous administration of IWP-247 reversed L-NAME-induced deficits in rats. In awake adult male rats, intravenous dosing of IWP-247 increased fMRI-BOLD signals above baseline in discrete brain areas including amygdala, hippocampus, thalamus, and reticular activating regions, compared to vehicle treated animals. By contrast, the peripherally restricted sGC stimulator (IWP-040) showed minimal effects on fMRI-BOLD signals with modest activation of regions including the amygdala, entorhinal cortex and ventral subiculum. Taken together, IWP-247, a CNS-penetrant sGC stimulator, increased regional CBF and activated brain regions involved in attention, learning and memory in nonclinical studies. These results support further evaluation of sGC as a therapeutic target for the treatment of neurological disorders.

Disclosures: C.J. Winrow: A. Employment/Salary (full or part-time):; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **J.E. Jones:** A. Employment/Salary (full or part-time):; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **P. Germano:** A. Employment/Salary (full or part-time):; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **S. Jacobson:** A. Employment/Salary (full or part-time):; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **S.S. Correia:** A. Employment/Salary (full or part-time):; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **K.W. Tang:** A. Employment/Salary (full or part-time):; Axial Biotherapeutics. **J. Tobin:** A. Employment/Salary (full or part-time):; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **R.R. Iyengar:** A. Employment/Salary (full or part-time):; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **P.P. Kulkarni:** None. **C.F. Ferris:** 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.; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Animal Imaging Research. F. Consulting Fees (e.g., advisory boards); Ironwood Pharmaceuticals. **M. Currie:** A. Employment/Salary (full or part-time):; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals. **J.R. Hadcock:** A. Employment/Salary (full or part-time):; Ironwood Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ironwood Pharmaceuticals.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.01/HHH35

Topic: H.02. Human Cognition and Behavior

Title: Distinct patterns of activity are associated with spatial memory encoding in the anterior but not posterior hippocampus

Authors: H. A. FRITCH, S. P. MACEVOY, B. M. JEYE, *S. D. SLOTNICK
Boston Col., Chestnut Hill, MA

Abstract: There are many hypotheses regarding specialization of the anterior versus posterior hippocampus including memory encoding versus retrieval, other cognitive processes versus spatial memory, and global spatial representations versus local spatial representations (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). In the present fMRI study, we aimed to evaluate whether the pattern of activity in the anterior hippocampus or the posterior hippocampus was associated with spatial memory encoding. During encoding, participants viewed abstract shapes in the center of each visual field quadrant while maintaining central fixation. During retrieval, old shapes were presented at fixation and participants identified the previous quadrant of each shape. A general linear model analysis revealed that accurate *retrieval* of shapes in each quadrant, exclusively masked by accurate memory for shapes in the other quadrants, produced a distinct activation in the hippocampus (Jeye, MacEvoy, Karanian, & Slotnick, 2018). A multi-voxel pattern analysis was conducted to assess whether there were distinct patterns of activity associated with *encoding* shapes in each quadrant within the anterior hippocampus (Talairach y-coordinates –20 to –9) or the posterior hippocampus (y-coordinates –33 to –22). On an individual participant basis, for each encoding quadrant, response patterns were split into halves by run (e.g., odd runs versus even runs) and then the patterns in one data half were classified based on patterns in the opposite half. A classifier was able to distinguish patterns evoked by items in each quadrant at significantly above chance accuracy in the anterior but not posterior hippocampus, and accuracy in the anterior hippocampus was significantly greater than accuracy in the posterior hippocampus. These findings indicate that spatial memory encoding of items presented in each visual field quadrant is associated with patterns of activity in the anterior but not posterior hippocampus, which supports the hypothesis that the anterior hippocampus is preferentially associated with encoding. Moreover, if the global-representation hypothesis of the anterior hippocampus is correct, the present results suggest participants did not encode the precise spatial location of each item during our task.

Disclosures: H.A. Fritch: None. **S.P. MacEvoy:** None. **B.M. Jeye:** None. **S.D. Slotnick:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.02/HHH36

Topic: H.02. Human Cognition and Behavior

Support: CIHR Grant 156070
CIHR CGS-Masters

Title: Human medial temporal lobe contributions to learned approach-avoidance conflict detection and resolution

Authors: *S. CHU, M. MARGERISON, S. THAVABALASINGAM, E. B. O'NEIL, R. ITO, A. C. H. LEE
Univ. of Toronto, Toronto, ON, Canada

Abstract: Human and rodent studies have highlighted a critical role for the anterior portion of the hippocampus (ventral in rodents) in the processing of learned approach-avoidance conflict, a scenario that arises when a stimulus is associated simultaneously with both positive and negative valences. It remains unclear, however, if this region contributes to the detection and/or resolution of approach-avoidance conflict. Moreover, relatively little work has examined the potential involvement of other medial temporal lobe structures. To address these issues, 20 neurologically healthy participants first learned to approach or avoid a series of single novel visual objects in a computerised game, with the goal of maximising their score. Approaching a positive object led to the gain of points, whereas approaching a negative object resulted in point loss. Conversely, avoiding a positive or negative object had no impact on a participant's score. Following successful learning, subjects were presented with pairs of these objects during fMRI scanning. Crucially, the objects within each pair possessed either the same valence (positive-positive or negative-negative, i.e. no approach-avoidance conflict) or different valences (positive-negative, i.e. high approach-avoidance conflict). On each trial, participants were required to respond to each pair by either (1) making an approach-avoid decision in order to score points (decision trials); (2) indicating whether the presented objects had the same or different valences (detection trials); or (3) following a visual instruction to approach or avoid (action trials). Comparing brain activity across these conditions allowed for the identification of regions involved in conflict resolution and detection. Within the medial temporal lobe, significant activity was observed in the anterior hippocampus and perirhinal cortex, with activity in these regions fluctuating according to the level of approach-avoidance conflict, and whether participants made an approach-avoidance decision as opposed to solely detecting the presence of conflict. Our findings provide further insight into learned approach-avoidance conflict processing and reveal differential contributions of the hippocampus and surrounding medial temporal lobe structures.

Disclosures: S. Chu: None. **M. Margerison:** None. **S. Thavabalasingam:** None. **E.B. O'Neil:** None. **R. Ito:** None. **A.C.H. Lee:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.03/DP14/HHH37

Topic: H.02. Human Cognition and Behavior

Support: Alfred und Anneliese Sutter-Stöttner Stiftung
Hedwig Widmer Stiftung

Title: Crossmodal integration performance is specifically related to medial perirhinal cortex thickness in very early Alzheimer's disease

Authors: *S. KRUMM[1], A. U. MONSCH[1,2], J. REINHARDT[4,5], R. W. KRESSIG[1,3], K. I. TAYLOR[1,2,6]
[1]Memory Clinic, Basel Univ. Ctr. for Med. of Aging, Felix Platter Hosp., Basel, Switzerland; [2]Fac. of Psychology, [3]Fac. of Med., Univ. of Basel, Basel, Switzerland; [4]Div. of Diagnos. and Interventional Neuroradiology, Univ. Hosp. Basel, Basel, Switzerland; [5]Dept. of Neuroradiology, Univ. Hosp. Zurich, Univ. of Zurich, Zurich, Switzerland; [6]Ctr. for Speech, Language and the Brain, Dept. of Exptl. Psychology, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Neuropsychological dysfunction in Alzheimer's disease (AD) is hypothesized to occur when neuropathology disrupts the functioning of the corresponding brain systems and compensation strategies fail. Although the clinical setting routinely applies well-established neurocognitive tests to track and diagnose AD, tasks that specifically measure the integrity of the cortical region first affected by neurofibrillary tau pathology (i.e. medial perirhinal cortex [mPRC]) are not yet readily available. In view of AD neuro-pathogenesis, measures of mPRC functioning may represent earlier cognitive markers of incipient AD than e.g. common episodic memory tests. We therefore identified a cognitive assessment of purported mPRC function, i.e. crossmodal integration of visual object representations and environmental auditory stimuli (Taylor et al., 2006). To test whether this task specifically reflects mPRC-related dysfunction in AD, we administered it to very early AD patients (n = 12; 10 male; mean MMSE score = 26.33 ± 1.56; mean age = 74.50 years ± 6.45; mean education = 15.25 years ± 2.42) and cognitively healthy normal controls (n = 21; 12 male; mean MMSE score = 29.05 ± 1.07; mean age = 68.81 years ± 11.49; mean education = 14.48 years ± 4.22). All participants were simultaneously presented with a color object photograph and an environmental sound (n= 40 trials in total). Participants had to decide as quickly as possible whether these two stimuli belong together or not (e.g., a picture of a cat and the sound 'miau'). High-resolution 3T magnetic resonance images were acquired from all participants. Regions first affected by neurofibrillary tau pathology (i.e. mPRC, lateral perirhinal cortex, and entorhinal cortex) were manually drawn on coronal slices of

the native space cortical surface reconstruction generated by FreeSurfer, according to anatomical landmarks described in Kivisaari et al. (2013). A linear regression with total intracranial volume as covariate revealed that only average cortical thickness in the left mPRC, but not cortical thickness of the lateral perirhinal cortex or entorhinal cortex, predicted performance on the crossmodal integration task: $F(2, 30) = 5.570$; $p = .009$; $R^2 = .271$; $\beta = 2.669$. These findings confirm that crossmodal integration is specifically associated with mPRC integrity, and suggest that this task may provide a very early marker of incipient AD.

Disclosures: S. Krumm: None. **A.U. Monsch:** None. **J. Reinhardt:** None. **R.W. Kressig:** None. **K.I. Taylor:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.04/HHH38

Topic: H.02. Human Cognition and Behavior

Support: Medical Research Service of the Department of Veterans Affairs I01CX001375

Title: Factors, other than amnesia, that predict performance on tests of news event memory

Authors: A. T. J. CAWLEY-BENNETT[1], I. E. ASP[1,2,3], S. GOLSHAN[3,1], *C. N. SMITH[1,3]
[1]Veterans Affairs San Diego Healthcare Syst., San Diego, CA; [2]Psychology, [3]Psychiatry, Univ. of California San Diego, San Diego, CA

Abstract: Damage to the medial temporal lobe (MTL) is associated with retrograde amnesia, that is, difficulty remembering information acquired prior to the onset of amnesia. Tests of notable public events (news events) are useful tools for measuring retrograde memory and assessing the severity of retrograde amnesia. Yet, memory for news events is likely to be influenced by factors other than amnesia. For example, how often one follows news events or the number of different sources one uses to learn about news events could affect performance. These types of factors may be problematic when interpreting retrograde amnesia in patients because one does not know if poor performance on the test results from brain injury or depends on factors unrelated to neuroanatomy, such as minimal exposure to news events. We tested recall and recognition memory for 60 notable news events that occurred in the recent past (from 2009 to 2017) in 150 healthy participants aged 25 to 82 using Amazon's Mechanical Turk. In addition to traditional participant characteristics (sex, age, education), we obtained subjective reports of the amount of exposure to news events (frequency of exposure to news events and the number of news sources used). We found that the amount of education, the frequency of exposure to news events, and the number of news event sources significantly predicted both recall and recognition

accuracy. Specifically, participants performed better if they had more education, frequent news exposure, and learned about news from many sources. Next, we compared the size of the effects on accuracy due to these participant characteristics to the size of the effect on accuracy due to amnesia in three memory-impaired patient groups: patients with bilateral hippocampal lesions (N=9), patients with large MTL lesions (N=2), patients with mild cognitive impairment (MCI; N=15, thought to be a transitional stage between healthy aging and Alzheimer's disease). We found that sizes of the effects of education (more educated vs. less educated), exposure frequency (frequent vs. not frequent), and number of sources (many sources vs. few sources) were similar to the size of the effect between control participants versus memory-impaired patients with hippocampal lesions or MCI. These results suggest that a number of factors can influence performance on tests of news events. Thus, poor performance in this type of test can result from having limited education or limited exposure to news events and not brain injury. Therefore, it is important to account for these factors when using tests of news event memory to determine the severity of retrograde amnesia in neurologic or psychiatric patients.

Disclosures: A.T.J. Cawley-Bennett: None. **I.E. Asp:** None. **S. Golshan:** None. **C.N. Smith:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.05/HHH39

Topic: H.02. Human Cognition and Behavior

Support: VA Grant I01CX000359
VA Grant I01CX001375
NIMH Grant 24600
NIH Training Grant 5T32AG000216

Title: Eye movements support the link between conscious memory and medial temporal lobe function

Authors: *Z. J. URGOLITES[1,4], C. N. SMITH[4,1], L. R. SQUIRE[4,1,2,3]
[1]Dept. of Psychiatry, [2]Dept. of Neurosciences, [3]Dept. of Psychology, UCSD, La Jolla, CA; [4]Veterans Affairs San Diego Healthcare Syst., San Diego, CA

Abstract: When individuals select the recently studied (and familiar) item in a multiple-choice memory test, they direct a greater proportion of viewing time towards the to-be-selected item when their choice will be correct than when their choice will be incorrect. Thus, for both correct and incorrect choices, individuals indicate that the chosen item is old, but viewing time

nevertheless distinguishes between old and new items. What kind of memory supports this preferential viewing effect? One possibility is that hippocampus-independent (unconscious) memory supports this effect because eye movements appear to reveal information beyond what is reflected in overt behavioral choice. Alternatively, conscious, hippocampus-dependent memory might support this effect. If so, the preferential viewing effect should be related to established measures of declarative memory (i.e., accuracy scores, confidence ratings, and response times). In Experiment 1, 30 young adults made three-alternative forced-choice recognition memory judgments for targets (200 photographs of scenes studied 30 min earlier) and foils (each target was presented together with two thematically-related novel scenes). They exhibited the preferential viewing effect: individuals looked longer at the selected item when it was correct than when it was incorrect. In addition, they were more confident and responded faster when their choice was correct than when their choice was incorrect. Moreover, the size of the preferential viewing effect was strongly correlated with recognition accuracy as well as with the differences in confidence ratings and in response times for correct and incorrect choices. Importantly, in four analyses that minimized the contribution of declarative memory in order to detect a possible contribution from other processes, preferential viewing of the old scene did not occur. Thus, the preferential viewing effect reflects conscious memory for which items are old and which items are new. In Experiment 2, five memory-impaired patients with medial temporal lobe lesions made recognition memory judgments for targets (100 photographs of scenes studied 1 min earlier) and foils. The patients exhibited poor recognition accuracy and reduced differences in confidence ratings and response times for correct and incorrect choices in comparison to controls. We conclude that the preferential viewing effect is a phenomenon of conscious, declarative memory and dependent on the medial temporal lobe. The findings support the link between medial temporal lobe function and declarative memory. When the effects of experience depend on the medial temporal lobe, the effects reflect conscious memory.

Disclosures: Z.J. Urgolites: None. **C.N. Smith:** None. **L.R. Squire:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.06/HHH40

Topic: H.02. Human Cognition and Behavior

Support: NIH R01 MH069456
NSF GRFP

Title: How does the hippocampus simultaneously learn episodes and regularities?

Authors: *B. SHERMAN, N. B. TURK-BROWNE
Psychology, Yale Univ., New Haven, CT

Abstract: Any given experience allows us to extract idiosyncratic details about that particular episode, as well as regularities that hold across related experiences. These mnemonic functions require fundamentally different computations: episodic memory employs sparse representations to keep similar experiences distinct, whereas statistical learning requires more overlapping representations to strengthen common elements. The tension between these competing functions was thought to be solved by mapping them onto distinct brain systems — the hippocampus for episodic memory and neocortex for statistical learning. However, this view has recently been challenged by empirical evidence of statistical learning in the hippocampus and by a computational model of the hippocampus that exhibits both episodic memory and statistical learning using different pathways. Although this latter model has been supported by studies that assessed episodic memory and statistical learning in isolation, both forms of learning likely occur in parallel. This raises the question of whether and how the hippocampus can simultaneously acquire information about episodes and regularities. One possibility is that episodic encoding may interfere with statistical learning (or vice versa), given their shared use of the CA1 subfield and of common input/output structures. Another possibility is that statistical learning improves predictability and provides richer temporal context, allowing for better encoding of idiosyncratic details. In two initial behavioral studies, participants viewed a stream of trial-unique scenes drawn from sequential category-level pairs (e.g., beach->mountain) and then were administered a surprise memory test. In Experiment 1, we found that recognition memory was significantly better for second, relative to first, items of a category pair. Importantly, this effect was specific to high-confident responses and emerged over the course of statistical learning. In Experiment 2, we collected temporal source judgments at test to ensure that we were probing hippocampal memory. Consistent with the previous experiment, the precision of source memory declined for first items encountered late vs. early during learning, whereas source memory for second items resisted such interference. Together, these data provide converging evidence of a synergistic relationship between episodic memory and statistical learning. Given these behavioral interactions, we are now using high-resolution fMRI to investigate the neural mechanisms of episodic memory and statistical learning within the hippocampus, including their interactions across subfields.

Disclosures: B. Sherman: None. **N.B. Turk-Browne:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.07/HHH41

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant EY021755
NIH Grant MH069456
NWO Rubicon Grant 446-15-004

Title: Distinct hippocampal representations of predicted features and objects

Authors: *L. RAIT, P. KOK, N. TURK-BROWNE
Yale Univ., New Haven, CT

Abstract: Sensory processing is strongly influenced by prior expectations. Expectations about both simple features (e.g., orientation) and more complex objects (e.g., shape) modulate processing in visual cortex. However, it is unclear whether these two kinds of expectations arise from the same top-down sources and operate via the same underlying mechanisms. To investigate this, we exposed human participants to complex auditory cues predicting either the orientation of a subsequent grating stimulus (Experiment 1, N=24), or the shape of an abstract Fourier descriptor object (Experiment 2, N=24). We measured brain activity using high-resolution functional magnetic resonance imaging (fMRI). We compared the influence of predictions about the orientation vs. shape. Using inverted encoding models, we found that expectations about both orientation and shape modulated visual cortex, facilitating processing of expected stimuli relative to unexpected stimuli. However, expectations about orientation and shape were represented differently from each other in the hippocampus. In Experiment 2, we found that the pattern of activity in the hippocampus contained a representation of the shape that was predicted by the auditory cue. However, this was not true for orientation in Experiment 1, where the pattern of activity in the hippocampus did not contain a representation of the orientation that was predicted by the cue. To interrogate the circuitry of these expectation signals further, we applied an automated segmentation method to distinguish subfields of the hippocampus. Where shape expectations were represented in CA3 (combined with CA2 and dentate gyrus), grating expectations were *negatively* represented in this subfield. These findings are especially striking given that the design of both experiments was identical, differing only in whether the visual stimuli were abstract shapes or oriented gratings. Finally, when oriented gratings were expected but omitted, the pattern of activity in V1 reflected the expected orientation, suggesting that such expectations can evoke a template of the predicted feature in sensory cortex. In contrast, this did not occur for shapes that were expected but omitted. Altogether, our findings suggest that expectations about low-level features and higher-level objects may involve distinct neural mechanisms.

Disclosures: L. Rait: None. **P. Kok:** None. **N. Turk-Browne:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.08/HHH42

Topic: H.02. Human Cognition and Behavior

Support: CIHR Grant No. 126105 awarded to MN Rajah
Alzheimer's Society of Canada Grant No. 1435 awarded to MN Rajah

Title: Volume of posterior hippocampus is positively related to object-location associative memory in healthy adults

Authors: J. SNYTTE[1], A. ELSHIEKH[1], R. K. OLSEN[3], L. MANNING[1], *M. N. RAJAH[2]
[1]Grad. Program in Neurosci., McGill Univ., Montreal, QC, Canada; [2]Psychiatry, McGill Univ., Verdun, QC, Canada; [3]Rotman Res. Inst., North York, ON, Canada

Abstract: The medial temporal lobes (MTL) are important for episodic memory. Yet, it remains unclear if specific regions of the MTL support memory for distinct features of an episodic event. In the current study we examined if individual differences in grey matter volumes of MTL regions were related to remembering object-location vs. object only information about past events in healthy individuals (N = 18; mean age = 21.41, mean years of education = 14.82). High resolution T2-weighted structural MRI images (TR 2500ms, TE 198 ms, 320 slices of 0.60 mm thickness, 0.64 x 0.64 x 0.64 mm voxels, FOV = 206) were obtained from each participant. We used a hybrid approach of manual segmentation using the OAP protocol (Olsen et al., 2013; Palombo et al., 2013) and the Multiple Automatically Generated Templates (MAGeT; Chakravarty et al., 2013) brain algorithm to measure the grey matter volume of the perirhinal, entorhinal and parahippocampal cortices, and anterior and posterior hippocampus. Participants also performed an object-location associative episodic memory task. Behavioral accuracy measures for associative (object-location) memory, recognition (object only) memory, misses, correct rejections and false alarms were calculated. Bivariate correlation analyses were conducted to determine if regional volumes correlated with specific mnemonic responses. We found that bilateral posterior hippocampal volumes were positively correlated to object-location memory (right, $r = +0.55$, $p = 0.02$; left, $r = +0.54$, $p = 0.02$) and negatively correlated with misses (right, $r = -0.48$, $p = 0.04$; left, $r = -0.47$, $p = 0.05$). No other significant correlations were observed, but data collection is ongoing. This study provides evidence for the role of posterior hippocampus in supporting object-location associations, and depicts a relationship between volume and cognition mediated by individual differences in healthy young adults.

Disclosures: J. Snytte: None. **A. Elshiekh:** None. **R.K. Olsen:** None. **L. Manning:** None. **M.N. Rajah:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.09/HHH43

Topic: H.02. Human Cognition and Behavior

Support: NRF-2018M3C1B8013690
NRF-2018M3C7A1022317

Title: Neural basis of episodic memory intermediate-term after medial temporal lobe resection

Authors: *W. JEONG[1,2], H. LEE[3], J. KIM[4], C. CHUNG[4,2]
[1]Dept. of Neurosurg., Seoul Natl. Univ. Hosiptal, Seoul, Korea, Republic of; [2]Neurosci. Res. Inst., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [3]Dept. of Mental Hlth. Res., Natl. Ctr. for Mental Hlth., Seoul, Korea, Republic of; [4]Dept. of Brain and Cognitive Sci., Seoul Natl. Univ. Col. of Natural Sci., Seoul, Korea, Republic of

Abstract: Purpose: How the brain supports intermediate-term preservation of memory in patients who underwent unilateral medial temporal lobe resection (MTLR) have not been demonstrated yet. To understand the neural basis of episodic memory intermediate-term after surgery for temporal lobe epilepsy (TLE), the relationship between the activation of hippocampus (HIP) during successful memory encoding and individual memory capacity was investigated in patients with MTLR.
Methods: Thirty-five adult patients who underwent unilateral MTLR at least 1 year before recruiting and who had a favorable seizure outcome were enrolled (17 left MTLR, 18 right MTLR; mean follow-up = 6.31±2.72 years). All patients underwent a standardized neuropsychological examination of memory function and functional MRI scanning with a memory encoding paradigm of words and figures. Activations of HIP during successful memory encoding were calculated and compared with standard neuropsychological memory scores, HIP volumes, and other clinical variables.
Results: Greater activation in HIP contralateral to resection was related to higher postoperative memory scores and greater postoperative memory improvement than the preoperative baseline in both patient groups. Specifically, postoperative verbal memory performance was positively correlated with contralateral right hippocampal activation during word encoding in the left surgery group. In contrast, postoperative visual memory performance was positively correlated with contralateral left hippocampal activation during figure encoding in the right surgery group. Activation of the ipsilateral remnant HIP was not correlated with any memory scores nor volumes of HIP; however, it had a negative correlation with the seizure onset age and positive correlation with the duration of illness in both patient groups.

Conclusions: For the first time, neural basis that support effective episodic memory intermediate-term after unilateral MTLR were characterized. The results provide evidence that the engagement of HIP contralateral rather than ipsilateral to resection is responsible for effective memory function intermediate-term (> 1 year) after surgery. Engagement of material-specific contralesional HIP, verbal memory for the left surgery group and visual memory for the right surgery group, was observed. Engagement of material-specific contralesional HIP, verbal memory for the left surgery group and visual memory for the right surgery group, was observed.

Disclosures: W. Jeong: None. **H. Lee:** None. **J. Kim:** None. **C. Chung:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.10/HHH44

Topic: H.02. Human Cognition and Behavior

Support: NRF-2018M3C7A1022317
NRF-2018M3C1B8013690

Title: Human episodic memory system is composed of several components served by specific temporal sub-regions: Insights from temporal lobe resection

Authors: *D. KIM[1], J. KIM[1], C. CHUNG[1,2,3]
[1]Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Dept. of Neurosurg., Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of; [3]Neurosci. Res. Inst., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Introduction: Medial temporal lobe structures are pivotal for episodic memory. However, it is still remained controversial whether certain temporal sub-regions are more crucial for specific aspect of episodic memory. Observation of post-operative changes in comprehensive neuropsychological tests in patients who underwent temporal lobe epilepsy surgery provides excellent chance to investigating organization of human memory system. Here, we analyze the relationship between the resection extent of each temporal sub-regions and the postsurgical memory changes in patients who underwent mesial temporal lobe epilepsy surgery. **Methods:** Included are 75 patients (left, n=43; right, n=32) with mesial temporal lobe epilepsy who underwent unilateral anteromedial temporal resection. Resection areas were manually delineated on each of patient's normalized MRI space. Then, we performed two forms of analysis. In the first one of region of interest analysis, we segmented resection areas into sub-regions using modified AAL atlas and investigated the correlation between resection volume of each temporal sub-region and memory test score changes. In the second one, we performed voxel based

statistical analysis that depends only on the resection maps regardless of segmentation into sub-regions to define the detail structures critical for specific memory sub-function. **Results:** In the verbal subtest that requires 30 minutes delayed recall of serial word list (15 word), the left lateral temporal region was related to post-operative memory decline. For the recognition of the same task, resection of left mesial and lateral temporal regions excluding hippocampus were associated with postoperative functional decline. For the verbal subtest in which patients learn 7 pairs of unrelated words, post-operative memory decline was correlated with resection of left hippocampus. **Conclusions:** We revealed that specific temporal sub-regions play specific role in verbal memory. These results can be explained by the two component left temporal model of verbal memory, a mesial protosemantic component operationalized as arbitrary paired associate learning that is 'context-rich' memory and a lateral semantic component operationalized as performance on which semantic structure can readily be imposed 'context-free' memory.

Disclosures: D. Kim: None. **J. Kim:** None. **C. Chung:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.11/HHH45

Topic: H.02. Human Cognition and Behavior

Title: Scaled environmental representations in the medial temporal lobe

Authors: *H. R. EVENSMOEN, H. RISE, L. RIMOL, A. K. HABERG
NTNU, Trondheim, Norway

Abstract: We do not store accurate representations of our environments, but scaled environmental representations that results in local clustering of environmental landmarks. The aim of this study was to investigate how these scaled environmental representations are encoded in the medial temporal lobe.
In this study, the participants (31 males) had to learn 35 small virtual environments, during functional magnetic resonance imaging (fMRI) at 3T (voxel size = 1.9x1.9x1.9mm, 32 channel head coil). The environments consisted of five objects that formed a unique positional pattern within the environments. Each environment was enclosed by one of 10 differently shaped outer walls. The participants were given 30 seconds with free exploration, followed by 15 seconds of poststimulus encoding, to learn each environment. This was followed by 15 seconds with odd-even judgements. The participants had to complete seven runs. Each run involved five environments. After each run, the participants' ability to associate the objects together, associate the objects with the outer wall, recreate the objects positional pattern, place the objects positional pattern relative to the outer wall, place the objects in their position within the positional pattern,

were tested for each environment.
Preliminary results showed that the activation in the posterior PHC, part of the parahippocampal place area, increased as the object landmarks scaled positional pattern became more accurate.

Disclosures: H.R. Evensmoen: None. **H. Rise:** None. **L. Rimol:** None. **A.K. Haberg:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.12/HHH46

Topic: H.02. Human Cognition and Behavior

Title: Auditory and visual mnemonic discrimination are correlated in healthy young adults

Authors: L. GIRAUD-CARRIER[1], D. K. BJORNN[1], C. TOWNE[2], *B. KIRWAN[1]
[1]Psychology, [2]Neurosci., Brigham Young Univ., Provo, UT

Abstract: Memory specificity is the ability to discriminate between similar memories. To date, research looking at memory specificity in humans has focused on visual stimuli and a direct comparison of performance on visual and auditory memory specificity is lacking. We conducted a behavioral experiment to determine if memory accuracy varies between auditory and visual sensory modalities. We also collected confidence rates to examine how subjective confidence in recognition memory judgments varied according to sensory modality. We hypothesized that memory specificity would be better with visual stimuli than auditory stimuli and that participants would be more confident of their answers to the visual stimuli.Data were collected from 154 healthy young adult participants, (79 male, 94 female). The task consisted of 8 blocks, alternating between 4 blocks of visual stimuli and 4 blocks of auditory stimuli, and each of the participants randomly receiving either visual or auditory stimuli first. Each block contained a study and a test portion. In the study portion participants were presented with novel stimuli and asked whether the stimulus is generally found “indoors” or “outdoors” to ensure attention to the stimulus during encoding. In the test portion, participants were presented with stimuli that were either the same or similar to those from the study portion. Participants gave combined recognition memory and confidence judgments as “definitely old,” “maybe old,” “maybe similar,” and “definitely similar.” Stimuli were presented for 2.5 seconds, the response period was 1.5 seconds, and an intertrial interval was 0.5 seconds.Performance on auditory and visual blocks were significantly correlated, but participants were able to discriminate visual stimuli significantly better than auditory stimuli. Confidence ratings were significantly higher for visual than for auditory stimuli as well. The findings of the present study give direct evidence that humans are better at discriminating visual memory than auditory memory over similar delays and similar levels of interference. The present study also develops the foundation for a task that

can be later used to examine hippocampal subfield activity using functional magnetic resonance imaging.

Disclosures: L. Giraud-Carrier: None. **D.K. Bjornn:** None. **C. Towne:** None. **B. Kirwan:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.13/HHH47

Topic: H.02. Human Cognition and Behavior

Support: Medical Research Service of the Department of Veterans Affairs Award #I01CS000359
NIMH Grant 24600

Title: Preferential viewing of changes in familiar scenes is impaired in patients with medial temporal lobe lesions but spared when they are (occasionally) aware of what has changed

Authors: C. N. SMITH[1,2], *L. R. SQUIRE[1,2,3,4]
[1]Veterans Affairs San Diego Healthcare Syst., San Diego, CA; [2]Psychiatry, [3]Neurosciences, [4]Psychology, UCSD, San Diego, CA

Abstract: There is disagreement about what kind of memory is impaired after damage to the medial temporal lobe (MTL). One idea is that the ability to acquire conscious memory is impaired. Another idea is that memory for relations or associations between items is impaired (i.e., regardless of conscious awareness for what has been learned). These ideas have been examined in studies of experience-dependent eye movements. For example, healthy individuals preferentially view the changed region of a familiar scene (i.e., the manipulation effect), and this effect is observed only when they are aware of what has changed. We examined the relationship between the manipulation effect and awareness in patients with MTL lesions. If the impairment reflects a loss of conscious memory, then patients should be impaired at explicitly identifying the manipulations, but they should exhibit the manipulation effect on the few occasions when they can identify what has changed. Alternatively, if the impairment reflects a loss of relational memory, then the manipulation effect should be absent regardless whether patients can identify what has changed. We tested eye movements and memory of scenes in controls and 5 memory-impaired patients with damage limited to the hippocampus or MTL. Participants viewed 12 familiar, repeated scenes and 12 familiar scenes where a change (manipulation) had been introduced. After viewing each scene, participants indicated if the scene was repeated or manipulated and then were asked to identify what had changed in each manipulated scene. The

patients were impaired at discriminating between repeated and manipulated scenes, and they identified many fewer of the manipulations than controls. In addition, across all manipulated scenes, controls tended to direct their viewing toward the region that had been changed (the manipulation effect), but the patients did not. Nevertheless, when eye movements were analyzed separately depending on whether participants were aware of the manipulation, MTL patients did exhibit the manipulation effect for the few scenes where they could identify what had changed (and the effect was absent when they could not identify what had changed). The manipulation effect is impaired in amnesia because the effect is observed only when participants are aware of the change and because memory-impaired patients are usually unaware of the changes. These findings are in agreement with the idea that awareness for what has been learned is a characteristic of hippocampus-dependent memory.

Disclosures: C.N. Smith: None. **L.R. Squire:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.14/HHH48

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01MH100121
NIH Grant R21HD083785
NIH Grant F32MH100904
NSF CAREER Award 056019
University of Texas Research Grant
Department of Defense, National Defense Science & Engineering Graduate Fellowship (NDSEG) Program

Title: Comparison of semi-automated hippocampal subfield segmentation methods in a pediatric sample

Authors: *M. L. SCHLICHTING[1], M. L. MACK[1], K. F. GUARINO[2], A. R. PRESTON[3]
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Loyola Univ. Chicago, Chicago, IL; [3]The Univ. of Texas at Austin, Austin, TX

Abstract: Episodic memory function has been shown to depend critically on the hippocampus. This region is made up of a number of subfields, which differ in both cytoarchitectural features and functional roles in the mature brain. Recent neuroimaging work in children and adolescents has suggested that these regions may undergo different developmental trajectories—a fact that has important implications for how we think about learning and memory processes in these

populations. Despite the growing research interest in hippocampal structure and function at the subfield level in healthy young adults, comparatively fewer studies have been carried out looking at subfield development. One barrier to studying these questions has been that manual segmentation of hippocampal subfields—considered by many to be the "gold standard" approach for defining these regions—is laborious and can be infeasible for large cross-sectional or longitudinal studies of cognitive development. Moreover, manual segmentation requires some subjectivity and is not impervious to bias or error. In a developmental sample of individuals spanning 6-30 years, we compared the performance of two semi-automated segmentation approaches, Advanced Normalization Tools (ANTs) and Automated Segmentation of Hippocampal Subfields (ASHS), to manual subfield delineation on each individual by a single expert rater. Across several quantitative metrics, we found negligible differences in subfield reliability across the child, adolescent, and adult age groups, suggesting that these methods can be reliability applied to developmental studies. We conclude that ASHS outperforms ANTs overall, and is thus preferable for analyses carried out in individual subject space. However, we underscore that ANTs is also acceptable, and may be well-suited for analyses requiring normalization to a single group template (e.g., voxelwise analyses across a wide age range). Previous work has validated the use of such methods in healthy young adults, as well as several special populations such as older adults and those suffering from mild cognitive impairment. Our results extend these previous findings to show that ASHS and ANTs can also be used in pediatric populations as young as six.

Disclosures: M.L. Schlichting: None. **M.L. Mack:** None. **K.F. Guarino:** None. **A.R. Preston:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.15/HHH49

Topic: H.02. Human Cognition and Behavior

Title: Behaviorally relevant events modulate hippocampal representations and functional connectivity

Authors: *R. MOYAL[1], H. B. TURKER[1], A. PHELPS[1], W.-M. LUH[2], K. M. SWALLOW[1]
[1]Dept. of Psychology, [2]Cornell MRI Facility, Cornell Univ., Ithaca, NY

Abstract: Events that are relevant for task performance may be differently encoded and represented in episodic memory systems than those that are not. For example, recent data indicate that stimuli that require an overt or covert response, such as a target in a detection task, boost memory for unrelated background items and their spatiotemporal context. In this rapid

event-related fMRI study, we examined the neural mechanisms underlying the effects of target detection on episodic memory encoding. Participants viewed a series of briefly presented, masked images from six different categories (male and female faces, beaches, forests, cars, and chairs). Whenever an image appeared, a high-pitched tone, low-pitched tone, or no tone was played. Participants memorized the images and pressed a button only when the tone was of a predefined target pitch. After scanning, they completed a recognition test on the images. If responding to behaviorally relevant events enhances episodic memory encoding, then the functional connectivity between hippocampus and visual areas should be greater on target than on distractor or no tone trials. The patterns of activity in regions involved in representing the current situation should also differ between tone type conditions. Consistent with the first prediction, Generalized Psychophysical Interaction (gPPI) analysis indicated that hippocampal activity was more strongly correlated with activity in visual cortex when a target tone was presented than in other conditions. Functional connectivity between hippocampus, thalamus, and dorsal striatum was also stronger on target tone trials. In addition, representational similarity analysis revealed that tone relevance modulated patterns of activity in the hippocampus and in visual cortex. These findings indicate that the hippocampus encodes ongoing events differently when they are task relevant. They also suggest that the detection of relevant events promotes integrated processing in a functional network spanning areas implicated in low-level perception and memory.

Disclosures: R. Moyal: None. **H.B. Turker:** None. **A. Phelps:** None. **W. Luh:** None. **K.M. Swallow:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.16/HHH50

Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant 24600
VA 5101CX000359

Title: Measures of episodic recollection for real-world events in patients with medial temporal lobe damage

Authors: *N. HEYWORTH[1,4], L. R. SQUIRE[4,1,2,3]
[1]Psychiatry, [2]Neurosciences, [3]Psychology, Univ. of California San Diego, La Jolla, CA; [4]VA Med. Ctr., San Diego, CA

Abstract: Studies of autobiographical memory have typically depended on retrospective methods. We studied autobiographical memory prospectively by taking patients with medial temporal lobe (MTL) damage and two control groups (CON-1 and CON-2) on a guided walk during which 11 planned events occurred. Memory for the events was assessed immediately after the walk for the patients and for CON-1-immediate, after one month for CON-2-1 month, and again after 2.6 years for CON-1-2.6 yrs. At test, participants delivered 6-min narrative recollections about the walk, gave 1-min narrations in response to a cue about each event, and took a multiple-choice test about the events. Patients recalled fewer details than CON-1-immediate and a similar number of details as CON-2-1 month and CON-1-2.6 yrs. The quality of the recollections was assessed using measures of episodic richness and other features of narrative construction including parts of speech, word frequency, imageability, and coherence. Coherence reflects the continuity and organization of the narrative and was measured by quantifying time-and-place information, as well as the chronology and theme of the narrative. Coherence was lower in patients than in all control groups largely due to poor chronology (i.e, the events of the walk were not recalled in chronological order). For most other measures, the episodic recollections reported by patients were similar to controls tested after long delays (1 month and 2.6 years), suggesting that the quality of the recollections was related to the strength of memory rather than factors specific to MTL function.

Disclosures: N. Heyworth: None. **L.R. Squire:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.17/HHH51

Topic: H.02. Human Cognition and Behavior

Support: R01 MH100121
T32 MH106454

Title: Hippocampal subfields show dissociable integration and separation signatures for overlapping memories

Authors: *R. J. MOLITOR, K. R. SHERRILL, N. W. MORTON, A. R. PRESTON
Univ. of Texas at Austin, Austin, TX

Abstract: The flexibility of episodic memory allows us to remember both the details that differentiate similar events as well as commonalities among overlapping experiences. These two functions are thought to arise through the formation of orthogonal memory codes via pattern separation and overlapping representations through memory integration, respectively. Empirical

research and computational modeling suggest that hippocampal subfields $CA_{2,3}$/dentate gyrus ($CA_{2,3}$/DG) are biased towards pattern separation, whereas CA_1 supports the formation of integrated memory codes. However, we have a limited understanding of the learning conditions that influence how highly similar memories are represented in hippocampal subfields. Here, we tested whether the formation of integrated and separated memories in hippocampal subfields depends on the strength of memory reactivation during learning. While some research suggests that reactivation may allow for the integration of new information into existing representations, other data suggest reactivation may lead to competition between co-active memories and require pattern separation to resolve interference. To adjudicate between these perspectives, participants studied a set of associations (AB pairs, either face-object or scene-object), and then were scanned with fMRI while they encoded overlapping associations (BC object-object pairs). Both before and after learning, participants were also scanned while viewing images (A and C) in isolation. Using multivariate techniques, we measured reactivation of related memories (A items) during overlapping event (BC) learning as well as the degree to which hippocampal activation patterns for indirectly related images (A and C) became less similar (i.e., separated) or more similar (i.e., integrated) after learning. We found evidence of a dissociation across hippocampal subfields, such that stronger reactivation led to the integration of overlapping memories in CA_1, and separation of those same memories in $CA_{2,3}$/DG. These findings provide insight into the basis of the complementary neural codes formed by the memory system and empirical support for computational learning models of the hippocampus.

Disclosures: R.J. Molitor: None. **K.R. Sherrill:** None. **N.W. Morton:** None. **A.R. Preston:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.18/HHH52

Topic: H.02. Human Cognition and Behavior

Support: ERC Consolidator Grant 647954

Title: Oscillatory theta dynamics and single unit activity in the human hippocampus during associative memory processing

Authors: *S. HANSLMAYR[1], R. CHELVARAJAH[3], D. ROLLINGS[4], V. SAWLANI[4], H. HAMER[5], S. GOLLWITZER[5], G. KREISELMEYER[5], P. R. ROELFSEMA[6], M. W. SELF[7], F. ROUX[2]
[2]Sch. of Psychology, [1]Univ. of Birmingham, Birmingham, United Kingdom; [3]Complex Epilepsy and Surgery Service, Neurosci. Department,, [4]Complex Epilepsy and Surgery Service, Neurosci.

Dept., Queen Elizabeth Hosp., Birmingham, United Kingdom; [5]Epilepsy Center, Dept. of Neurol., Univ. Hosp. Erlangen, Erlangen, Germany; [6]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [7]NIN, Amsterdam, Netherlands

Abstract: There is good agreement that theta oscillations in the human hippocampus play a central role for episodic memory formation. However, conflicting results have been reported on how theta power modulations are related to memory formation. Some studies reported theta power increases (putatively reflecting neural synchronization), whereas other studies reported theta power decreases (putatively reflecting neural de-synchronization) during memory formation. Therefore the question arises as to how theta power changes and neural synchronization processes underlie episodic memory formation in humans. To address this question we have recorded local field potentials and putative single-unit activity using microwire electrodes implanted in human patients suffering from epilepsy. Our results indicate that there is a significant band limited and sustained theta power increase during memory formation. This theta power increase, however, was limited to areas which also show an increase in firing rate during the task. Areas which do not show increased firing rates during the encoding task appear to show theta power decreases. Furthermore, our results suggest that in areas which show an increase in firing rate, the firing of neurons is weakly coupled to the phase of theta oscillations. These results suggest that both, theta power increases and decreases can be observed during memory formation, however, theta power increases are limited to areas which show an increase in firing rate. Theta power increases further might point towards neural synchronization processes in the service of memory formation. These results potentially resolve a current debate in the field in suggesting that whether we see theta power increases or decreases depends on whether recordings are obtained from areas which also show an increase in local spiking activity.

Disclosures: S. Hanslmayr: None. **R. Chelvarajah:** None. **D. Rollings:** None. **V. Sawlani:** None. **H. Hamer:** None. **S. Gollwitzer:** None. **G. Kreiselmeyer:** None. **P.R. Roelfsema:** None. **M.W. Self:** None. **F. Roux:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.19/HHH53

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R00 AG036845
NIH Grant R21 AG049968

Title: Cardiorespiratory fitness predicts default mode network effective connectivity in young adults

Authors: *K. L. KERN[1], C. A. KRONMAN[2], R. K. NAUER[3], M. F. DUNNE[1], T. W. STORER[4], K. SCHON[1]
[1]Dept. of Anat. and Neurobio., [2]Div. of Grad. Med. Sci., Boston Univ. Sch. of Med., Boston, MA; [3]Dept. of Psychological and Brain Sci., Boston Univ., Boston, MA; [4]Men's Health, Aging, and Metabolism Unit, Brigham and Women's Hosp., Boston, MA

Abstract: Rodent and human studies examining exercise-induced changes in brain structure indicate that the hippocampus, a brain region critical for episodic memory, demonstrates striking plasticity in response to exercise. Human studies examining exercise-induced changes in behavior demonstrate that exercise affects broad cognitive domains reliant on large-scale brain networks not limited to the hippocampal memory system. Examining network activity in large-scale resting-state brain networks may provide a link between exercise-induced hippocampal plasticity and cognitive enhancement. Previously, cardiorespiratory fitness (CRF) has been associated with enhanced functional connectivity of the default mode network (DMN). However, how CRF affects strength and directionality of connectivity, or effective connectivity, between the hippocampus and other DMN nodes remains unknown. We used resting-state fMRI and Conditional Granger Causality Analysis (CGCA) to test the hypothesis that CRF positively predicts effective connectivity between the HC and other DMN nodes in healthy young adults. Twenty-five participants (aged 18-35 years) underwent a treadmill test to determine CRF and a 10-minute resting-state fMRI scan (Philips 3T Achieva) to examine DMN effective connectivity. The DMN was identified using group independent component analysis, and effective connectivity between nodes was examined using CGCA. Linear regression analysis demonstrated that CRF significantly predicts strength of effective connectivity from the hippocampus to multiple DMN hubs, including the medial prefrontal, posterior cingulate, and lateral temporal cortices. These findings suggest functional connectivity changes between the hippocampus and large-scale brain networks as a link between the exercise-induced hippocampal plasticity observed in rodents and the exercise-induced enhancement of broad cognitive domains observed in humans.

Disclosures: K.L. Kern: None. **C.A. Kronman:** None. **R.K. Nauer:** None. **M.F. Dunne:** None. **T.W. Storer:** None. **K. Schon:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.20/HHH54

Topic: H.02. Human Cognition and Behavior

Support: Alberta Innovates Health Solutions Polaris Award

NSERC RGPIN-2017-03857
NSF Grant 1631465
DARPA Grant FG20678 440880/24900
NIH Grant R37NS21135, PI: Robert T. Knight with subaward to JJL).

Title: Sharp wave ripple cross-structure phase locking to cortical oscillations predicts the modulation of cortical activity in human intracranial recordings

Authors: *I. SKELIN[1], J. ZHENG[2], H. ZHANG[4], B. L. MCNAUGHTON[5], J. LIN[3]
[1]Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Dept. of Biomed. Engin., [3]Dept. of Neurol., Univ. of California, Irvine, Irvine, CA; [4]Biomed. Engin., Univ. of California Irvine, Irvine, CA; [5]Dept. of Neurosci., The Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: Hippocampal sharp wave/ripples (SWRs), cortical slow oscillations (SOs) and sleep spindles (SPs) have been proposed to support memory consolidation during the slow wave sleep (SWS). In particular, SWRs provide the time window for hippocampal memory reactivation and promote hippocampal-cortical communication supporting memory consolidation. However, it is less clear how hippocampal SWRs interact with cortical SOs/SPs during the SWS and how such interplay shapes cortical neuronal dynamics. To address this, we performed overnight intracranial electroencephalography recordings in 11 patients undergoing pre-surgical seizure localization. Specifically, we assessed the dependence between the cortical peri-SWR high frequency local field potential (HF-LFP; 300-900Hz) and SWR phase-locking to SOs and/or SPs in the same cortical location. Local field potential (LFP) was simultaneously recorded from the hippocampus, temporal, frontal and cingulate cortices. SWS periods were identified based on LFP delta (1-4 Hz) power in the frontal cortex. SWRs were identified based on double threshold of power in 80-150 Hz range (peak and duration). Periods surrounding interictal epileptic discharges (IEDs; +/- 1 s) were excluded from the analysis. Significance of HF-LFP response during -250 to 250 ms period surrounding the SWR peaks was based on the presence of significant difference from the baseline in at least two consecutive 25 ms time bins. Instantaneous phases of SOs and SPs at the SWR peak times were extracted from cortical LFP using the Hilbert transform. SWR-SO or SWR-SP cross-structure phase locking significance was assessed using Rayleigh test for non-uniformity of circular data. We found that the cortical locations showing significant HF-LFP response were more likely to show significant SWR phase locking to SOs or SPs, relative to cortical locations without significant HF-LFP response. This pattern was consistent for both anterior and posterior hippocampal SWRs (chi-square test; all p's < 0.02). These findings suggest that during SWS, SWR/SW/SP interactions orchestrate the dynamics of cortical HF-LFP, a proxy of multi-unit neuronal firing. This could represent an important mechanism for organizing hippocampal-cortical interactions supporting memory consolidation.

Disclosures: I. Skelin: None. **J. Zheng:** None. **H. Zhang:** None. **B.L. McNaughton:** None. **J. Lin:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.21/HHH55

Topic: H.02. Human Cognition and Behavior

Support: NIH NRSA F32AG054204

Title: Spontaneous generalized memory representations following paired-associates training

Authors: *S. ASHBY, C. R. BOWMAN, D. ZEITHAMOVA
Univ. of Oregon, Eugene, OR

Abstract: Memory studies typically focus either on memory for individual experiences (specificity) or the ability to link information across events (generalization). However, experiences in our daily lives are not neatly separated into specificity vs. generalization tasks. Instead, we have to make different judgments based on the same experiences. Do we spontaneously extract generalized knowledge even when the task at hand demands specificity? To answer this question, we assessed behavioral and neural measures of memory specificity and generalization during and after a task where participants learned face-name associations. Face stimuli were constructed as 50/50 blends of never-seen "parent" faces. Three parent faces were selected to determine category membership, presented as a family surname, and then blended with other parent faces. Each training face had a unique first name. As a result, the training faces had an underlying category structure that was incidental to the paired-associate learning as participants were instructed to memorize the full name for each face during fMRI. To measure specificity, participants completed a full name recall test and an old/new recognition task with novel face-blends as foils. Results showed good performance on both metrics, indicating that participants successfully acquired memory for specific faces. To measure generalization, participants made pairwise similarity ratings of faces before and after learning and made categorization judgments of novel face-blends. Results showed above-chance categorization of novel faces and greater perceptual similarity ratings for faces from the same category than different categories (controlling for physical similarity) that emerged after learning, indicating spontaneous acquisition of generalized knowledge. Neural pattern similarity analysis in the ventromedial prefrontal cortex (vmPFC) showed representations of individual items, but not categories, during the paired-associates training; category information was present in vmPFC during subsequent categorization but not recognition. These results indicate that vmPFC may flexibly access specific or generalized memory representations based on the current task demands. In contrast, perceptual regions like fusiform cortex showed category effects during both recognition and categorization, reflecting primarily perceptual information irrespective of

the task. This study demonstrates spontaneous formation of generalized knowledge even when task demands emphasized specificity and newly suggest a flexible role of vmPFC in representing both specific or generalized information in response to task demands.

Disclosures: S. Ashby: None. **C.R. Bowman:** None. **D. Zeithamova:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.22/HHH56

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery Grant 03637
NIH Grant 1U54MH091657
McDonnell Center for Systems Neuroscience at Washington University

Title: Hippocampal characteristics influence the structure of idle thought

Authors: *J. TSENG[1], J. POPPENK[2]
[1]Neurosci., [2]Psychology, Queen's Univ., Kingston, ON, Canada

Abstract: We are estimated to spend up to half of our waking hours in idle thought. Is this experience similar for everyone? Recent research has found that hippocampal damage changes the content and form of mind-wandering. Although brain damage could influence cognition in many ways, this finding raises the interesting possibility that, among healthy adults, individual differences in memory recall that are supported by the hippocampus influence the nature of traversal through mental states. Accordingly, we explored the role of the hippocampus by correlating its characteristics with neural markers of mental state traversal.
We conducted our analysis on 815 healthy participants between the ages of 22 and 35 years from the Human Connectome Project (HCP) dataset. Each participant had one hour of resting state functional MRI data. The HCP conducted group functional connectivity analyses to identify a specified number of brain region networks or “nodes”. Then, a participant’s mental state could be characterized as the linear combination of the activity at each node. As the HCP generated these representations for multiple sets of nodes, we carried out our analysis on the 15-, 100-, and 300-node timeseries.
The node timeseries for each participant was fed into the t-distributed stochastic neighbour embedding dimensionality reduction algorithm, which produced a two dimensional trajectory of the participant’s resting state brain activity. Then, we calculated the Euclidean distance between successive points in the lower dimensional output. We defined the duration of a state as the number of consecutive timepoints whose Euclidean distance from the previous timepoint falls

under a reasonable threshold. Using this definition, we determined the average and maximum time spent in each mental state and the number of state transitions. This was repeated for all participants and all three node timeseries.
We discovered that the three characteristics had small but significant correlations with hippocampal volume. In particular, the average time spent in a state was correlated with the right hippocampal volume (rs > 0.12, ps < 0.001), and the right anterior hippocampus (rs > 0.09, ps < 0.032). The findings held across the 15-, 100-, and 300-node timeseries, as well as across varying distance thresholds used to define the state transitions.
These results suggest that the hippocampus serves a role not only in episodic memory processes, but also in the very structure of thought, perhaps influencing our thought trajectories by means of episodic reinstatement.

Disclosures: J. Tseng: None. **J. Poppenk:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.23/HHH57

Topic: H.02. Human Cognition and Behavior

Support: NIH NRSA F32AG054204

Title: Distinct connectivity patterns along the hippocampal anterior-posterior axis

Authors: *L. FRANK
Univ. of Oregon, Eugene, OR

Abstract: Recent work suggests that memories can be represented in the hippocampus at different levels of specificity. Hierarchical organization of memories may be supported by functional distinctions between the anterior and posterior hippocampus, such that detailed representations become increasingly more abstract as they move from posterior to anterior subregions. Animal studies have shown that the size of receptive place fields increase moving from dorsal (posterior) to ventral (anterior) hippocampus. In the episodic memory domain, human fMRI studies have shown small time-integration windows and sentence-level representations in the posterior, compared to larger time-integration windows and narrative-level representations in the anterior hippocampus. Additionally, we recently showed that activity in the anterior hippocampus uniquely reflected abstract concepts rather than specific category exemplars during a category generalization task. Given the different functions of the anterior and posterior hippocampus, we tested whether intrinsic functional connectivity differs between these hippocampal subregions. Similar to the proposed organization of the hippocampal axis, we

expected to see greater anterior hippocampal connectivity with medial prefrontal regions that are known to support generalizing across events and greater posterior hippocampal connectivity with lateral prefrontal regions involved with differentiation of overlapping events. We also tested how connectivity patterns may change or remain stable under varying levels of task engagement. Following category training, participants underwent fMRI, including a rest scan, two scans of passive viewing of category exemplars, and four runs of a category generalization task. Contrasts of anterior and posterior hippocampal connectivity revealed greater anterior hippocampal connectivity with the ventromedial prefrontal cortex, and greater posterior hippocampal connectivity with the dorsolateral prefrontal cortex and anterior cingulate cortex. These patterns remained stable across the three phases (rest, passive viewing, concept generalization), suggesting the organization of connectivity is relatively unaffected by level of task engagement. These results contribute to our understanding of functional organization along the long axis of the hippocampus, highlighting interactions with distinct prefrontal regions that contribute to differentiating details or finding commonalities respectively.

Disclosures: L. Frank: None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.24/HHH58

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery Grant 03637
CFI-JELF Grant 35008

Title: Interactions of hippocampal characteristics with sleep structure in gist memory consolidation

Authors: *N. MATORINA, G. MARVEL, J. POPPENK
Psychology, Queen's Univ., Kingston, ON, Canada

Abstract: Recent research in animal models suggests that the hippocampus increases in spatial scale when moving from its dorsal to ventral segments, which is analogous to the anterior and posterior segments in humans. This functional specialization may relate to more general memory features, such that the anterior hippocampus is specialized for 'gist' memories, and the posterior for 'detailed' memories. Interestingly, a growing body of research suggests that sleep may be involved in the process of abstracting detail information into gist, or gist extraction. However, the role of the anterior hippocampus in the relationship between sleep physiology and gist memory is unknown.

In the current, pre-registered study, we collected sleep, memory and neuroanatomical data from 66 participants. The memory sessions took place in the evening before sleep, in the morning after sleep (12 hours later), and 7 days later. Participants wore a portable EEG device between the evening session and morning session that measured and classified sleep at home. We investigated two kinds of gist memory in a visual statistical learning (VSL) and a transitive inference (TI) task. For VSL, participants were tested on sequences of shapes. Some shapes were presented in the same order each time (detail sequences), while others were presented in the same order only 3/4 of the time (gist sequences). For TI, participants studied pairs of associates and were tested on studied pairs (detail pairs), as well as unstudied pairs that required inferences from studied pairs (gist pairs). Finally, neuroanatomical volumes were estimated through Freesurfer analysis of 0.7mm isotropic whole-brain T1w and T2w data, which were gathered using a 3T MRI scanner. To control for head size, we residualized the effects of intra-cranial volume.
We predicted that either more slow-wave sleep (SWS) or more rapid-eye movement (REM) sleep would improve gist memory over time. We also predicted that anterior hippocampal volume would moderate this relationship, such that those with more SWS or REM and larger anterior hippocampal volumes would have more improvement in gist memory over time. Using multi-level modelling, we found a variety of interactions. As predicted, SWS positively predicted gist memory over time in VSL for participants with larger left anterior and smaller left posterior hippocampi.
Conversely, in our TI task, right anterior hippocampal volume positively predicted gist memory only in participants with low levels of REM. This suggests that anterior hippocampal volume and SWS may be synergistic in consolidation of gist for extracting visual patterns, while REM may impede consolidation of gist for inferences.

Disclosures: N. Matorina: None. **G. Marvel:** None. **J. Poppenk:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.25/HHH59

Topic: H.02. Human Cognition and Behavior

Support: EU Joint Programme Neurodegenerative Disease Research

Title: Preliminary results of the Hippocampal Subfields Group harmonized protocol for segmenting human hippocampal subfields on 3T MRI

Authors: *V. A. CARR[1], R. LA JOIE[2], R. K. OLSEN[3], L. E. M. WISSE[4], K. M. C. AMUNTS[5], J. C. AUGUSTINACK[6], A. BAKKER[7], A. R. BENDER[8], D. BERRON[9], S. L. DING[10], A. C.

BURGGREN[11], R. DE FLORES[12], M. CHAKRAVARTY[13], A. D. EKSTROM[14], P. KANEL[15], O. KEDO[16], R. INSAUSTI[17], N. V. MALYKHIN[18], S. G. MUELLER[2], N. OFEN[20], J. B. PLUTA[4], D. J. PALOMBO[22], D. SCHOEMAKER[13], C. E. L. STARK[23], T. STEVE[19], L. WANG[25], M. A. YASSA[24], Q. YU[21], P. A. YUSHKEVICH[4], A. M. DAUGHERTY[20]
[1]Psychology, San Jose State Univ., San Jose, CA; [2]UCSF, San Francisco, CA; [3]Rotman Res. Inst., North York, ON, Canada; [4]Univ. of Pennsylvania, Philadelphia, PA; [5]Res. Ctr. Juelich, Juelich, Germany; [6]Radiology, Massachusetts Gen. Hosp., Charlestown, MA; [7]Psychiatry and Behavioral Sci., Johns Hopkins Univ., Baltimore, MD; [8]Dept. of Epidemiology & Biostatistics, Michigan State Univ., East Lansing, MI; [9]Clin. Res. Unit, Lund Univ., Lund, Sweden; [10]Allen Inst. for Brain Sci., Seattle, WA; [11]Semel Neuropsychiatric Inst., UCLA, Los Angeles, CA; [12]Univ. of Caen, Normandy, France; [13]McGill Univ., Montreal, QC, Canada; [14]UC Davis, Davis, CA; [15]Florida State Univ., Tallahassee, FL; [16]Res. Ctr. Jülich, Jülich, Germany; [17]Sch. of Medicine, HNL, Univ. of Castilla-La Mancha, Albacete, Spain; [18]Biomed. Engin., [19]Univ. of Alberta, Edmonton, AB, Canada; [21]Inst. of Gerontology, [20]Wayne State Univ., Detroit, MI; [22]Univ. of British Columbia, Vancouver, BC, Canada; [24]Neurobio. and Behavior, [23]Univ. of California Irvine, Irvine, CA; [25]Psychiatry, Northwestern Univ., Chicago, IL

Abstract: Over the last 15 years, the number of studies using high-resolution MRI to examine the structure and function of human hippocampal subfields has soared. However, the ability to compare findings across studies has been hampered by substantial differences in how subfields are segmented by different research groups. To remedy this issue, the Hippocampal Subfields Group (HSG) was formed in 2013 with the goal of creating a valid and reliable harmonized segmentation protocol grounded in robust histological standards. Over the past 5 years, our efforts have focused on developing a harmonized protocol for high-resolution T2-weighted 3T MRI. Our development approach consists of: 1) collecting histology samples labeled by multiple anatomists to guide the development of an MRI segmentation protocol, 2) holding working group meetings to develop different portions of the protocol (e.g., hippocampal body, head), 3) assessing HSG agreement with boundary rules via a series of online questionnaires, 4) revising boundary rules in response to questionnaire responses, and 5) testing reliability of each rule on multiple MRI data sets. Given substantial differences in the anatomy of the hippocampal head and body, we have approached these regions separately. For both the body and the head, we have completed steps 1 and 2, such that we have developed a preliminary subfield segmentation protocol for each region. Additionally, with respect to the outer boundaries of the body (i.e., the anterior/posterior, medial/lateral, and superior/inferior boundaries), we have completed steps 3 and 4 as well. An online questionnaire describing each of the outer boundary rules was sent to HSG members, with a total of 29 labs participating. Consensus agreement was reached for all rules included in the questionnaire, but slight modifications were made to select rules to improve clarity. We are now in the process of creating and administering additional questionnaires assessing agreement with the inner boundary rules for the hippocampal body (e.g., between the cornu ammonis fields) as well as the boundary rules for the hippocampal head. Upon completion of the assessment/revision process for each set of rules, the final phase - validation testing - will begin. Once completed, the harmonized protocol is expected to significantly impact the field by enabling cross-study comparisons and thus advancing our understanding of the structure and function of hippocampal subfields.

Disclosures: V.A. Carr: None. **R. La Joie:** None. **R.K. Olsen:** None. **L.E.M. Wisse:** None. **K.M.C. Amunts:** None. **J.C. Augustinack:** None. **A. Bakker:** None. **A.R. Bender:** None. **D. Berron:** None. **S.L. Ding:** None. **A.C. Burggren:** None. **R. de Flores:** None. **M. Chakravarty:** None. **A.D. Ekstrom:** None. **P. Kanel:** None. **O. Kedo:** None. **R. Insausti:** None. **N.V. Malykhin:** None. **S.G. Mueller:** None. **N. Ofen:** None. **J.B. Pluta:** None. **D.J. Palombo:** None. **D. Schoemaker:** None. **C.E.L. Stark:** None. **T. Steve:** None. **L. Wang:** None. **M.A. Yassa:** None. **Q. Yu:** None. **P.A. Yushkevich:** None. **A.M. Daugherty:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.26/HHH60

Topic: H.02. Human Cognition and Behavior

Support: MRC Grant G030011765439
MRC Grant G100227698624

Title: Semantic learning in developmental amnesia: Can recognition facilitate recall?

Authors: *R. ELWARD[1], J. LIMOND[2], M. MISHKIN[3], F. VARGHA-KHADEM[4]
[1]Univ. Col. London, London, United Kingdom; [2]Univ. of Exeter, Exeter, United Kingdom; [3]NIMH, Bethesda, MD; [4]UCL Inst. of Child Hlth., London, United Kingdom

Abstract: Patients with developmental amnesia (DA) have suffered hippocampal damage in infancy and subsequently shown poor episodic memory (i.e. amnesia for the events of their life). Despite their high IQs, these patients underperform in school presumably because they do not remember their prior lessons and learning experiences, and must therefore rely on acontextual semantic knowledge which is accrued over time. It is not clear how patients with DA are able to amass this bank of general knowledge in the presence of episodic amnesia. One important factor is that patients with DA show well-developed recognition memory on multiple choice or true/false tests. These recognition abilities may support semantic learning. We provide data from three experiments designed to understand how patients with DA learn semantic information. The first experiment showed that multiple learning trials on new texts did not facilitate recall. In this study, patients were presented with four texts containing new knowledge. Each text was presented six times and followed by cued recall after each trial. Recall performance remained low (<40%) and plateaued after the 3rd trial. One week later, patients recalled only 35% of the contents (controls recalled 80%) in a cued recall test. In experiment two, the same knowledge test was presented to a new group of patients with DA via video. Each video was presented six times and after each trial, a multiple-choice recognition test was administered. Patients performed at 90% accuracy during these recognition tests. One week later, patients with DA

were able to recall 85% of the learned information in a cued recall test. These data show that multiple opportunities to recognise the new information led to good recall performance. Experiment three directly compared recognition learning versus recall learning. A patient with DA (aged 8 years) watched each video six times. Two videos were supported with cued recall tests and two were supported with recognition tests. One week later, cued recall performance was compared across the two learning paradigms. This showed a clear benefit of recognition learning compared to recall learning (35% vs. 76%). If this finding replicates in a larger group of patients, then it may provide a practical means of supporting the education of young people with DA. Furthermore, the data suggest that young people with extensive hippocampal damage indeed utilise their recognition memory to support the integration of new information into their semantic system.

Disclosures: R. Elward: None. **J. Limond:** None. **M. Mishkin:** None. **F. Vargha-Khadem:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.27/HHH61

Topic: H.02. Human Cognition and Behavior

Support: CIHR Project Grant 148839

Title: Similarities in perirhinal cortex response patterns related to decision outcome in recognition-memory judgments

Authors: *A. BLUMENTHAL[1], C. B. MARTIN[2], S. KOHLER[3]
[1]Univ. of Western Ontario, London, ON, Canada; [2]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada; [3]Univ. Western Ontario, London, ON, Canada

Abstract: The ability to determine whether objects and other entities in the environment are novel or familiar is known to depend on perirhinal cortex (PrC) in the medial temporal lobes. However, how PrC representations support item-based recognition-memory decisions is not fully understood at present. Previous fMRI work from our laboratory has revealed that PrC carries category-specific memory signals for a number of visual object categories, including faces, chairs, and planes. In the present study, we re-examined data from these studies to determine how such such signals relate to the decision outcome. Specifically, we asked whether patterns of activity in PrC reflect perceived or objective memory status, and how similarities in these patterns correspond to decision outcome. We found that pattern similarities in PrC were higher for items from the same category that had the same perceived memory status (familiar vs novel).

By contrast, similarities did not vary according to objective item status. This set of result did not hold for the hippocampus, whose patterns showed no relationship to perceived or objective memory status. We also found that PrC patterns associated with false alarms were more similar to hits than those associated with correct rejections were to hits (despite their shared objective memory status as novel). These similarity relationships, however, were only present when items from the same category were compared in the analyses. Critically, the latter result suggests that similarities in PrC response patterns for hits and false alarms during recognition-memory decisions are not tied to shared motor-responses. Instead, they appear to be tied to computations that inform the process of memory discrimination. Inasmuch as PrC is thought to contribute to discrimination through 'global matching', our findings suggest that this matching is constrained by category membership.

Disclosures: A. Blumenthal: None. **C.B. Martin:** None. **S. Kohler:** None.

Poster

693. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe I

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 693.28/III1

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery Grant 03637
CFI-JELF Grant 35008
Queen's University Research Initiation Grant

Title: Anterior and posterior hippocampal contributions to extraction of schematic information from naturalistic experiences

Authors: *J. POPPENK, N. DOAN, J. WASERMAN, I. PETRAR-SILCA
Psychology, Queen's Univ., Kingston, ON, Canada

Abstract: Interest has grown in functional subdivisions within the human hippocampus, with the anterior portion of the structure believed to feature a role in gist-like episodic memories, and the posterior a role in detailed episodic memories. While the hippocampus as a whole is believed to contribute to consolidation of episodic memories into more schematized forms over time, how these segments may individually contribute to this process is not well understood. Notably, the anterior, but not posterior hippocampus features direct connections to the anterior temporal lobe and ventromedial prefrontal cortex, two regions believed to feature schematic representations. We therefore predicted that the anterior hippocampus in particular, with its gist-like features, could feature a role in memory generalization, whereas discretized event data in posterior hippocampus may serve to feed such generalization.

To explore this possibility, we gathered memory and neuroimaging data from 66 healthy young adults (age 25-35). Participants viewed six 13-slide narrated slideshows, each comprising a short event. The first slide of slideshow was a "context" slide featuring a location for the event and corresponding soundscape. Immediately after seeing the slideshow as well as the next day, participants were cued with the context slide and soundscape and asked to recall the corresponding slideshow. Participants were given two minutes for recall of each slideshow, and were asked to verbally recall each event slide-by-slide, in order, and in as much detail as possible. On a later occasion, participants repeated this task with an additional six slideshows. These recall attempts were scored by raters for schematic elements, slide gist and slide detail content. At the end of our experiment, neuroanatomical volumes were estimated through Freesurfer analysis of 0.7mm isotropic whole-brain T1w and T2w data, which were gathered using a 3T MRI scanner. To control for head size, we residualized the effects of intra-cranial volume.
To link memory and brain data, we performed mediation analyses, investigating changes to memory representations after a delay as a function of hippocampal characteristics. These analyses revealed a positive relationship between the left pHPC/aHPC ratio and development of schematic memory representations in the delayed condition. *Post hoc* analyses revealed that, contrary to our expectations, the driver of this relationship was the left hippocampal tail. We speculate that these results reflect the posterior hippocampus's role in maintaining distinctive representations of events from which schematic representations may be generated.

Disclosures: J. Poppenk: None. **N. Doan:** None. **J. Waserman:** None. **I. Petrar-Silca:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.01/III2

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Grid realignment predicts human contextual memory

Authors: *L. C. SOMMER, J. B. JULIAN, C. F. DÖLLER
Kavli Inst. For Systems Neuroscience, NTNU, Trondheim, Norway

Abstract: To guide spatial behaviour successfully, the brain must retrieve memories that are appropriately associated with different navigational contexts. Grid cells in the entorhinal cortex

(EC) may serve an important role in this function. Between navigational contexts, grid cells alter their firing patterns, a process known as grid realignment. However, the relationship between grid realignment and contextual memory is unclear. One possibility is that grid realignment is driven purely by changes to perceptual cues. Alternatively, grid realignment may reflect memory for navigational context *per se* that goes beyond sensory processing. To test the relationship between grid realignment and contextual memory, human participants learned the locations of target objects in two virtual reality arenas (Context A and B) distinguished by the shape of their boundaries (one square, one circle) and their distal orientational cues. Following training, participants underwent fMRI scanning while object location memory was tested in Contexts A and B, as well as in a third ambiguous half-square half-circle arena (Context AB). By comparing the recalled target object locations in Context AB to the correct target locations in Context A versus B, we could estimate which contextual memory (Context A or B) was reinstated in Context AB on a trial-by-trial basis. Preliminary results showed greater changes in the human EC fMRI grid-like signal across Contexts A and B than across different trials within the same context, consistent with contextual grid realignment in humans. Critically, we also found that the EC grid-like signal predicted contextual memory retrieval in Context AB. Together, these results provide the first evidence for grid cell involvement in contextual memory independent of sensory processing.

Disclosures: L.C. Sommer: None. **J.B. Julian:** None. **C.F. Döller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.02/III3

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Temporal mapping in the human entorhinal cortex

Authors: *J. L. BELLMUND[1], L. DEUKER[2], C. F. DOELLER[1]
[1]Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway; [2]Ruhr-University, Bochum, Germany

Abstract: Episodic memories are thought to be formed by binding events to their spatial as well as temporal context and medial temporal lobe structures have been implicated in the formation of such integrated memories. But which neural mechanisms allow us to remember when a specific

event occurred? Theoretical accounts and recent empirical evidence suggest that the entorhinal cortex provides a slowly varying temporal signal, which might enable the tagging of individual events in time; thereby allowing the formation of a temporal mnemonic map. Here, we probe the development of temporal representations in the entorhinal cortex through learning. We relate changes in multi-voxel pattern similarity in entorhinal cortex to temporal distances between events participants encountered through repeated navigation along a fixed route in a large-scale urban environment. FMRI data were acquired during isolated presentation of events in random order, indicating that the observed similarity structure reflects the reactivation of a learned temporal mnemonic map rather than time per se. Our findings speak to how the entorhinal cortex might provide temporal context information for episodic memory and elucidate the mechanisms underlying the mapping of time in the medial temporal lobe in general.

Disclosures: J.L. Bellmund: None. **L. Deuker:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.03/III4

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Creating an artificial memory context alters associative memory formation

Authors: *S. H. COLLIN[1,2], P. VAN DEN BROEK[2], T. VAN MOURIK[2], P. DESAIN[2], C. F. DOELLER[3,2]
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Donders Institute, Radboud Univ., Nijmegen, Netherlands; [3]Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway

Abstract: Memory is affected when humans voluntarily modulate single neuron or neural population activity using neurofeedback. However, it is currently unknown whether memory is facilitated or impaired after such neural perturbations. In this study, participants memorized objects while we trained them to modulate their brain activity patterns in the medial temporal lobe (MTL), hereby creating an artificial memory context in the MTL while memorizing objects. The results revealed that the context created by neurofeedback caused interference with memory performance during a subsequent associative learning task. These results shed light onto how memory formation can be influenced by synthetic memory tags with neurofeedback, with

implications for our understanding of mnemonic coding in the MTL and possible applications in information technology as well as the clinic.

Disclosures: S.H. Collin: None. **P. van den Broek:** None. **T. van Mourik:** None. **P. Desain:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.04/III5

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Mapping the human navigation network with high-field fMRI: A voxel-wise encoding model

Authors: *M. NAU, T. NAVARRO SCHRÖDER, C. F. DOELLER
Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway

Abstract: The brain's navigation system has been extensively studied over decades, yet on a population and systems level the underlying spatial codes remain poorly understood. Here, we used 7T-fMRI to monitor human brain activity at submillimeter resolution while participants navigated a virtual environment and performed an object location memory task. We predicted each voxel's time course by incorporating navigation behavior into computational models of neural tuning curves for which weights were estimated using cross-validated ridge regression. By iterating this procedure for a multitude of parameters (e.g. tuning width) and by predicting held-out data, this approach allows us to map each voxel's tuning and predictability across the cortex. Preliminary results point towards a wide-ranging network coding participants' virtual head direction and give new perspectives on grid-like fMRI signatures in the human mediotemporal lobe. While we implemented this model using human fMRI navigation data, it yields the potential to be used also for other human imaging techniques, cognitive domains or for data from other species.

Disclosures: M. Nau: None. **T. Navarro Schröder:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.05/III6

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Decoding spatial behavior from raw hippocampal activity using deep learning

Authors: *M. FREY[1], S. TANNI[2], T. NAVARRO SCHRÖDER[1], C. BARRY[2], C. F. DOELLER[1]
[1]Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway; [2]UCL, London, United Kingdom

Abstract: Spatially modulated cells in the hippocampus and medial enthorinal cortex (mEC) provide reliable information required for successful navigation in an environment. A lower information limit of these structures can be approximated by assessing the accuracy with which self-location can be decoded from the underlying neural activity. Most traditional decoding algorithms use spike sorting methods for detecting action potentials which are subsequently used for spatial decoding. However, spike sorting potentially introduces selection biases and methods limited to action potentials inevitably discard information contained in the local field potential (LFP). Here we decode self-location from wide-band (2Hz - 6000Hz) electrophysiological signals from regions CA1 and mEC in freely moving rats, using state-of-the art deep learning algorithms. We demonstrate that our model is able to extract spatially relevant features from wide-band traces and outperforms established location-decoding methods, such as a Bayesian decoder, trained on manually sorted spikes. We further investigated if this decoding architecture generalises to non-rodent data, specifically to human brain activity recorded using magnetoencephalography (MEG) during navigation in a virtual environment. This allows us to examine single-cell as well as population level activity underlying spatial navigation in rodents and humans within a single model.

Disclosures: M. Frey: None. **S. Tanni:** None. **T. Navarro Schröder:** None. **C. Barry:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.06/III7

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Electrophysiological markers of grid cell population activity across species

Authors: *T. NAVARRO SCHRÖDER[1], M. MØRREAUNET[1], M. NAU[1], T. STAUDIGL[2], J. B. JULIAN[1], J. BELLMUND[1], J.-M. SCHOFFELEN[2], C. F. DOELLER[1,2,3]
[1]Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway; [2]Donders Institute, Radboud Univ., Nijmegen, Netherlands; [3]Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany

Abstract: Grid cells in the rodent and human entorhinal cortex are a critical component of the brain's spatial coding system. In virtual-reality (VR) navigation tasks in humans, the fMRI BOLD signal in the entorhinal cortex exhibits hexadirectional modulations that may reflect population activity of grid cells. However, it remains unknown whether and how grid cell population activity specifically gives rise to this hexadirectional hemodynamic fMRI signal. Here we address this issue in two steps. First, we employed a VR navigation experiment using magnetoencephalography (MEG) in human participants and found hexadirectional signal modulations in the high-gamma band, source-localised to the medial temporal lobe. Next, we conducted analyses to test the relationship between grid cell activity and local field potential (LFP) recordings in freely moving rats. We found hexadirectional modulations in the same frequency band as in the human MEG navigation experiment. The orientation of this hexadirectional LFP modulation was aligned to the orientation of the hexagonally symmetric firing patterns of grid cells. Together, these findings describe new ways to measure grid cell population activity and their non-invasive source localisation using MEG. Crucially, we link grid cell activity to measures of population activity in rats and humans, thereby elucidating the physiological basis of non-invasive grid cell population measures previously revealed with fMRI. Since grid cell function is affected early in Alzheimer 's disease, understanding how to measure their activity with non-invasive methods is of high clinical relevance.

Disclosures: T. Navarro Schröder: None. **M. Mørreaunet:** None. **M. Nau:** None. **T. Staudigl:** None. **J.B. Julian:** None. **J. Bellmund:** None. **J. Schoffelen:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.07/III8

Topic: H.02. Human Cognition and Behavior

Support: ERC-CoG GEOCOG 724836
ERC-StG 261177
NWO-Vidi 452-12-009

Title: Knowledge transfer between physical and conceptual spaces

Authors: *D. KUHRT, J. L. S. BELLMUND, C. F. DOELLER
Kavli Inst. For Systems Neuroscience, NTNU, Trondheim, Norway

Abstract: Spatial navigation is a basic cognitive process known to involve the hippocampal-entorhinal system. Research on spatial navigation in rodents has revealed a range of functionally defined cell types, among them place and grid cells conveying positional information. These studies typically investigate navigation in spaces based on the three physical dimensions by tracking movements through physical enclosures or virtual environments. Therefore, we will refer to these spaces as physical spaces. Intriguingly, recent studies have shown spatial processing mechanisms in abstract, conceptual spaces beyond navigation in physical space. This is in line with the notion that these conceptual spaces can be described by the same quantifiable features as physical space and further suggests that representations of abstract information in higher-level brain areas might follow coding principles identified in spatial navigation research. Here, we ask the question if knowledge acquired in physical and conceptual spaces is represented in a similar format, allowing knowledge transfer between spaces. To test this hypothesis, we created a 2D conceptual space and a corresponding virtual model of a physical space, carefully matching space-defining features such as dimensionality, size, underlying metric, shape and informational content. In an object-location memory paradigm, participants learned to navigate both spaces using the same controls and successfully created object-location associations. In a post-learning test, we probed participants' abilities to transfer knowledge between the two spaces. Behavioural results provide evidence for accurate representations of both spaces as well as for a transfer of knowledge between spaces. Future fMRI analyses will shed light on the representation of knowledge gained in physical and conceptual spaces in the brain's navigation system and the potential neural integration of information across spaces. Our initial behavioural findings speak to the growing body of evidence suggesting domain-generality of spatial coding principles in higher-level cognition.

Disclosures: D. Kuhrt: None. **J.L.S. Bellmund:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.08/III9

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Deformed navigation in ageing

Authors: *A. M. WINTHER[1], J. L. S. BELLMUND[1], S.-C. LI[2], N. W. SCHUCK[3], C. F. DOELLER[1]
[1]Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway; [2]Lifespan Developmental Neurosci., Fac. of Psychology, TU Dresden, Dresden, Germany; [3]Max Planck Inst. For Human Develop., Berlin, Germany

Abstract: A hallmark of Alzheimer's disease (AD) is the impaired ability to find one's way through the environment. One of the first structures affected in AD is the entorhinal cortex (EC), a structure containing grid cells, known for their importance in the brain's spatial navigation system. Old transgenic EC-TAU mice express impairments in grid cell function. In humans, both old adults and healthy young participants with an increased genetic risk for AD, i.e., *APOE*-ε4 carriers, exhibit weaker hexadirectional entorhinal signals, understood to be an fMRI signature of grid cell population activity, compared to young controls. Carriers of this genetic risk factor differ from controls and apply a strategy characterized by reduced navigation in the central area of a virtual testing environment. Here, we investigate differences in navigational strategies in young and old healthy volunteers performing an object-location memory task, while undergoing fMRI, to gain insight into processes underlying cognitive ageing affecting spatial navigation and memory. Following an initial encoding phase, in which participants explored the locations of objects in a virtual environment, participants were cued to recall and further learn the object locations. Our findings indicate differences in navigational strategies between the age groups, with old adults navigating more frequently farther away from the centre of the environment, thereby indicating a surround navigational strategy compared to young participants. Further, our paradigm enabled dissociation of mnemonic strategies for positional learning through the movement of a local landmark in a subsequent memory test. Our behavioural findings will be complemented by analyses of neural representations during navigation contrasting the age groups. Understanding alterations in memory and navigation in healthy ageing may contribute to distinguish normal from pathological cognitive ageing in dementia diseases such as AD.

Additionally, it may enable investigations of AD pathology, as structures known to be important for memory and spatial navigation are affected at early stages of the disease.

Disclosures: A.M. Winther: None. **J.L.S. Bellmund:** None. **S. Li:** None. **N.W. Schuck:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.09/III10

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: The role of hexadirectional coding in spatiotemporal integration

Authors: *I. POLTI[1], M. NAU[1], V. VAN WASSENHOVE[2], C. F. DOELLER[1]
[1]Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway; [2]CEA, DRF/Joliot, NeuroSpin; INSERM, U992, Cognitive Neuroimaging Unit, Univ. Paris-Sud; Univ. Paris-Saclay, Gif-Sur-Yvette, France

Abstract: The hippocampal-entorhinal network has been implicated in processing spatial as well as temporal information. Convergent evidence from single-unit recordings in non-human primates and fMRI in humans suggested that entorhinal cortex represents a grid-like map of visual space. This spatial code is hexadirectional, as reflected in a six-fold rotationally symmetry of neural activity as a function of gaze direction. However, the behavioural function of this code and whether and how it incorporates information about time into underlying computations remain elusive. Here, we designed a highly controlled visual tracking task in which participants fixated at a dot that moved on linear trajectories with different speeds within a circular boundary. Whenever the dot stopped moving, participants had to estimate the time-to-contact (TTC), i.e. the time point when the dot would have hit the boundary if it continued moving. This allowed us to examine TTC estimates as a function of gaze direction for a variety of target durations while participants' eye movements were monitored using high-resolution eye tracking. Preliminary results suggest that TTC estimates indeed depend on gaze-direction and that our task is well suited to examine time-judgement effects, such as scalar variability across the visual field. We now investigate whether participants' behavioural performance is related to fMRI activity in the hippocampal formation (HF), in particular entorhinal cortex. Our novel psychophysics approach has the potential to provide new insights into how space and time are processed dynamically

across the visual field and could help to unravel HF involvement in spatiotemporal integration and prospection.

Disclosures: I. Polti: None. **M. Nau:** None. **V. van Wassenhove:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.10/III11

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Mapping conceptual space

Authors: *S. THEVES[1], G. FERNANDEZ[1], C. F. DOELLER[2]
[1]Donders Institute, Radboud Univ., Nijmegen, Netherlands; [2]Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway

Abstract: The hippocampal formation encodes maps of the physical environment. Whether its spatial coding principles provide a universal metric for organizing non-spatial information, such as conceptual knowledge, remains elusive. Here we investigate how the human hippocampus represents knowledge using a novel concept-learning paradigm combined with functional neuroimaging. Participants learned to categorize objects based on the relation of two abstract stimulus-feature dimensions that span a two-dimensional concept space with the diagonal as category boundary. We seek to investigate the neural representations of both, the conceptual space, as well as resulting categorical information. So far, we showed that following learning, two-dimensional distances between individual positions in concept space were represented in the hippocampal multi-voxel pattern as well as in the univariate hippocampal signal as indexed by fMRI adaptation. This suggests a map-like format of neural concept representations and supports the notion that the hippocampus computes domain-general, multidimensional cognitive maps along continuous dimensions.

Disclosures: S. Theves: None. **G. Fernandez:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.11/III12

Topic: H.02. Human Cognition and Behavior

Support: SNSF P300P1_174450
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009
ERC-StG 261177

Title: Theta phase coordinated memory reactivation reoccurs in a slow-oscillatory rhythm during NREM sleep

Authors: *T. STAUDIGL[1], T. SCHREINER[1], C. F. DOELLER[2], O. JENSEN[3], B. RASCH[4]
[1]Donders Institute, Radboud Univ., Nijmegen, Netherlands; [2]Kavli Inst., NTNU, Trondheim, Norway; [3]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom; [4]Dept. of Psychology, Univ. of Fribourg, Fribourg, Switzerland

Abstract: It has been proposed that sleep's contribution to memory consolidation is to reactivate prior encoded information. To elucidate the neural mechanisms carrying reactivation-related mnemonic information, we investigated whether content-specific memory signatures associated with memory reactivation during wakefulness reoccur during subsequent sleep. We show that theta oscillations orchestrate the reactivation of memories, irrespective of the physiological state. Reactivation patterns during sleep autonomously re-emerged at a rate of ~1 Hz, indicating a coordination by slow oscillatory activity

Disclosures: T. Staudigl: None. **T. Schreiner:** None. **C.F. Doeller:** None. **O. Jensen:** None. **B. Rasch:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.12/III13

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Value inference across cognitive maps

Authors: *M. M. GARVERT[1], N. SCHUCK[2], C. F. DOELLER[3]
[1]Max Planck Inst. For Human Cognitive and Brain, Leipzig, Germany; [2]Max Planck Inst. For Human Develop., Berlin, Germany; [3]Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway

Abstract: It has been suggested that the brain organises knowledge about the relationships between positions in space and non-spatial information in a cognitive map. Such a representation of events and knowledge may facilitate goal-directed behaviour by enabling the generalisation of value across related states. Here, we combine a novel virtual reality task with computational modeling to investigate whether humans generalise across related states to infer reward values that were never directly experienced. In this task, spatial relationships between stimuli learned on day 1 predict reward relationships in a decision making task on day 2. We find that participants not only update the stimulus-reward associations they experience directly, but also use their knowledge about the relationships between stimuli to predict outcomes of cues whose values were not experienced. Relational knowledge organised in cognitive maps can thus be used to extrapolate across related states and thereby facilitate novel inference. By including stimuli in the decision making task whose spatial locations are unknown, we further demonstrate that novel stimuli can be integrated into existing cognitive maps if their statistical structure is consistent with previously experienced regularities. Furthermore, the prediction errors subjects experience when they first learn about a stimulus position predict how much participants like stimuli at the end of the experiment, suggesting a close relationship between spatial learning and stimulus valuation. Using fMRI, we investigate the neural dynamics underlying the spread of values across cognitive maps in hippocampal-medial prefrontal networks. Together, our novel approach opens up the possibility to connect seemingly disparate fields of spatial coding, learning and decision behaviour.

Disclosures: M.M. Garvert: None. **N. Schuck:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.13/III14

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Temporal dynamics of event integration

Authors: *L. S. SCHURMANN[1], J.-M. SCHOFFELEN[1], S. H. COLLIN[2], B. MILIVOJEVIC[1], C. F. DOELLER[3]
[1]Donders Institute, Radboud Univ., Nijmegen, Netherlands; [2]Princeton Neurosci. Inst., Princeton, NJ; [3]Kavli Inst., NTNU, Trondheim, Norway

Abstract: Memory integration is a crucial building block of autobiographical memory. It enables us to weave individual events of our daily lives into coherent memory networks. Furthermore, it allows us to dynamically and flexibly reorganize these mnemonic networks when new information becomes available. Results from our previous fMRI study (Milivojevic et al., 2015) provided evidence for a central role of the hippocampal-prefrontal circuit in memory integration using life-like stimuli. However, while both areas are known to be involved, the contribution of individual regions and the related temporal dynamics remain unclear. In this study, we extended the life-simulating memory paradigm used in our previous studies (Milivojevic et al., 2015; Collin et al., 2015) in order to shed light on the temporal dynamics of hippocampal and prefrontal processing underlying memory integration. In a life-like narrative-insight task, we presented three seemingly unrelated events per narrative, which participants saw several times in a counterbalanced order during a pre-insight phase and a post-insight phase. Between these phases we showed a fourth event in isolation, which provided insight into which of the previously seen events belong together in a narrative and which event does not. This allowed us to track insight-triggered reconfiguration of these event networks. We extended the paradigm to include a behavioral relatedness judgment task, in which participants rated how related events were, both before and after the insight phase, for each of the 13 narratives they saw. This enables us to track the brain-behaviour relationship for each of the narratives in a within-subject design. Additionally, in order to examine hierarchical embedding of event networks into broader, across-narrative networks, we included a task designed to assess the relationship between the individual narratives. This task will give us novel insights into both behavioral and neural correlates of across-narrative integration, and extend our previous work on hierarchical memory networks (Collin et al., 2015). In addition, we optimized the paradigm to examine the temporal aspects of memory integration using MEG (data acquisition ongoing). A possible mechanism that might underlie memory integration is prefrontal-hippocampal theta coupling (Backus et al., 2016). Using representational similarity analysis, we will examine how memory integration varies on different temporal scales within and across trials. This study offers the opportunity to improve our understanding of how the human brain is able to apply prior knowledge to inform our behavior in new situations.

Disclosures: L.S. Schurmann: None. **J. Schoffelen:** None. **S.H. Collin:** None. **B. Milivojevic:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.14/III15

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Functional parcellation of the rodent and human hippocampus at 7T

Authors: *A. G. DAHL, S. A. HUBER, T. NAVARRO SCHRÖDER, C. F. DOELLER
Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway

Abstract: The hippocampus is a region pivotally involved in spatial navigation and memory formation. While most of the tools available for functional magnetic resonance imaging (fMRI) analysis have been developed for human data, much of what we know about the underlying mechanisms for spatial navigation comes from rodent research. To facilitate translation between rodent and human research we take advantage of a novel, data-driven method from human fMRI analysis to estimate individual functional connectivity maps for each voxel within the rodent hippocampus. Computing the similarity between these 'fingerprints' results in a hippocampal map of functional connectivity similarity, which is then subjected to a manifold learning algorithm, yielding topographies of functional connectivity change across hippocampal voxels. Finally, by applying a clustering algorithm we identify functional subunits within the hippocampal formation based on their similarity in connectivity to the rest of the brain. We then compare the results with those obtained from applying the same method to a human 7T fMRI dataset, allowing us to investigate translational features between the functional connectivity of the rodent and human hippocampus.

Disclosures: A.G. Dahl: None. **S.A. Huber:** None. **T. Navarro Schröder:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.15/III16

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177
ERC-CoG GEOCOG 724836
NWO-Vidi 452-12-009

Title: Evidence for a discretized organization of the hippocampal long-axis in humans

Authors: *S. A. HUBER[1,2], T. NAVARRO SCHRÖDER[1], A. KOBRO-FLATMOEN[1], J. SCHWARZBACH[2], M. P. WITTER[1], C. F. DOELLER[1]
[1]Kavli Inst. for Systems Neuroscience, NTNU, Trondheim, Norway; [2]Univ. Regensburg, Regensburg, Germany

Abstract: The hippocampus is a medial temporal lobe structure that is critically involved in numerous brain functions including memory formation, spatial navigation and emotional processing. Its involvement in this multiplicity of cognitive functions raises the question to what extent this diversity is reflected in the functional anatomy of the hippocampus. Previous studies point towards two opposing hypotheses, namely a smooth functional gradient versus discrete step-like transitions along the longitudinal axis of the hippocampus.
Here, we present evidence for a discretized organization of the hippocampal long-axis. Our findings are based upon a recently developed analysis algorithm applied to a high-resolution 7 Tesla functional magnetic resonance imaging (fMRI) dataset, incorporating 22 healthy adults. The algorithm consists of the following steps: First, the individual functional connectivity profiles of all hippocampal voxels to the rest of the brain are computed. Then, we estimate correlation coefficients between all pairs of voxel-wise connectivity 'fingerprints', yielding a functional connectivity similarity map of the hippocampus. This map is fed to a manifold learning algorithm to determine the topography of functional connectivity change within the hippocampus. Our results indicate that the dominant mode of functional connectivity change follows the hippocampal long-axis in a step-like, discretized manner. Finally, we used *k*-means clustering to parcellate the dominant mode of functional connectivity change into separate clusters.
Together with previous insights from gene expression studies, our findings support the hypothesis of a discretized organization of the hippocampal long-axis in humans.

Disclosures: S.A. Huber: None. **T. Navarro Schröder:** None. **A. Kobro-Flatmoen:** None. **J. Schwarzbach:** None. **M.P. Witter:** None. **C.F. Doeller:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.16/III17

Topic: H.02. Human Cognition and Behavior

Title: Memory interaction and integration in young and aged adults

Authors: *K. E. TOBIN[1], T. T. TRAN[2], A. R. PRESTON[3], A. BAKKER[1]
[1]Psychiatry and Behavioral Sci., Johns Hopkins Sch. of Med., Baltimore, MD; [2]Psychological & Brain Sci., Johns Hopkins Univ., Baltimore, MD; [3]Ctr. for Learning and Memory, The Univ. of Texas At Austin, Austin, TX

Abstract: Episodic memory formation is a dynamic process, where existing memories can be combined and updated with new and relevant experiences. The integration of prior experiences and new information allows us to create novel associations that support new inferences. This memory integration process requires both stable and reliable episodic memory representations as well as the flexibility to manipulate, combine, and incorporate new information.
Memory integration has been primarily examined in young adults but may play a significant role in age-related memory changes as well. Previous studies suggest that in older adults, episodic memories may be less stable and more prone to interference or be more rigid and less accessible for memory integration. The current study assessed memory integration and inferential reasoning in young adults and cognitively normal older adults using an associative inference paradigm. Our findings show that episodic memories remain stable in older adults but are inflexible with older adults showing difficulty integrating new information and generating new inferences when compared to young adults.

Disclosures: K.E. Tobin: None. **T.T. Tran:** None. **A.R. Preston:** None. **A. Bakker:** 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.; AGENEBIO.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.17/III18

Topic: H.02. Human Cognition and Behavior

Title: Memory for Object identity and object positions in novel environmental scenes

Authors: *T. T. TRAN[1], K. E. TOBIN[2], V. PULIYADI[1], M. GALLAGHER[1], A. BAKKER[2]
[1]Psychological & Brain Sci., Johns Hopkins Univ., Baltimore, MD; [2]Psychiatry and Behavioral Sci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Subregions of the medial temporal lobe are differentially affected in healthy aging and Alzheimer's disease. Notably, the lateral entorhinal cortex appears particularly vulnerable in both normal and pathological aging. The lateral entorhinal cortex is one of the first sites of tau neurofibrillary tangle accumulation, a biomarker of Alzheimer's disease. However, even in cognitively normal older adults, the lateral entorhinal cortex shows considerable neurofibrillary deposits compared to young adults, suggesting that even in healthy aging, lateral entorhinal cortex functioning may be affected.
Although previous behavioral and neuroimaging studies in humans have examined the role of lateral entorhinal cortex in object identity memory, there is limited work on object position memory. Single-cell recordings in rodents have implicated lateral entorhinal cortex in object position memory as well as tracking a change in the position of an object in an environment. The current study examined behavioral differences between young and older adults in recalling object identity or object position within a computerized novel spatial environment. Results show that age-related changes in the function of lateral entorhinal cortex are exhibited through both decreased object identity and object position memory in older adults compared to younger adults. These results suggest that even in healthy aging these aspects of memory that depend on the lateral entorhinal cortex can be observed.

Disclosures: T.T. Tran: None. **K.E. Tobin:** None. **V. Puliyadi:** None. **M. Gallagher:** 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.; Agenebio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Agenebio. **A. Bakker:** 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.; Agenebio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Agenebio.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.18/III19

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R37NS21135, PI: Robert T. Knight with subaward to Jack J. Lin

Title: Medial temporal-medial prefrontal theta phase synchrony binds human associative memory

Authors: *H. ZHANG, J. ZHENG, J. LIN
Biomed. Engin., Univ. of California Irvine, Irvine, CA

Abstract: The hippocampus is critical for binding of distinct elements to form episodic memory. It has shown that theta rhythms in the hippocampus orchestrate the temporal coding of events but how hippocampal theta rhythm interact with other cortical and subcortical region such as the medial prefrontal cortex and amygdala to promote correct and incorrect associative memory is unknown. To investigate the amygdala-hippocampal-medial frontal prefrontal circuit dynamics during memory association, we recorded local field potential (LFP) simultaneously from the amygdala-hippocampus-orbitofrontal network in patients undergoing pre-surgical seizure localization. Patients performed a memory association task, in which they passively viewed pairs of images during the encoding phase, followed by the retrieval phase where the subjects were asked to discriminate whether the given pair is a correct association shown during the encoding phase.

We found that the hippocampal theta power significantly increased for success encoding compared to unsuccessful encoding (1s after stimulus onset, t-test $p<0.05$). To assess the connectivity in the amygdala-hippocampal-medial prefrontal circuit, we calculated the phase-locking value (PLV) and found distinct connectivity matrix for success encoding and unsuccessful encoding. Specifically, the medial temporal-medial prefrontal PLV in the theta band showed increased connectivity during correct encoding compared to incorrect encoding. In contrast, the connectivity between amygdala and hippocampus showed increased connectivity for incorrect versus correct associations. These findings demonstrate that although hippocampal theta synchrony is critical for associative memory, distinct cortical-subcortical circuit synchrony promotes correct and incorrect associations.

Disclosures: H. Zhang: None. **J. Zheng:** None. **J. Lin:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.19/III20

Topic: H.02. Human Cognition and Behavior

Title: Effect of repeated immediate reactivation on memory performance

Authors: *M. E. MONTCHAL, M. YASSA
UC Irvine, Irvine, CA

Abstract: Decades of memory research have underscored the importance of the hippocampus and medial temporal lobe cortex for memory retrieval. However, it remains unclear how memories and the brain networks supporting them change with time and experience. Converging evidence suggests that memories can shift from being dependent on the hippocampus to the cortex (Squire, 1992; Frankland and Bontempi, 2005). However, it is unknown how repeated retrieval events and the passage of time may interact to affect memory accuracy, especially of event details. Recent work has provided evidence that memory reactivation during sleep (Oyarzun, Moris, Luque, et al., 2017; Shimizu, Connolly, Cellini, et al., 2018) and during wakefulness (Tambini, Berners-Lee, and Davachi, 2017) can improve memory performance. Based on evidence-based models of memory, it is possible that memory reactivation can impair memory performance in certain circumstances. The Competitive Trace Theory (CTT) framework (Yassa and Reagh, 2013) holds that each reactivation of a memory causes it to become less episodic and more semantic. Taken to the extreme, this would mean that repeated reactivation immediately after a memory is formed would cause it to lose episodic detail and become more semantic. The current study aimed to test the influence of immediate repeated reactivation on memory for episodic details. Participants watched a video clip and were randomly assigned to either the reactivation group or the control group. The reactivation group viewed still frames from the video every 10 minutes and was instructed to imagine the scenes depicted. The control group viewed still frames from a video they had not seen. The extent of spontaneous reactivation was also measured using a questionnaire. We report accuracy for detailed and more generalized questions for both groups, elucidating the effects of repeated immediate reactivation on memory retrieval.

Disclosures: M.E. Montchal: None. **M. Yassa:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.20/III21

Topic: H.02. Human Cognition and Behavior

Support: NIA P50 AG16573

Title: Hippocampal cingulum white matter integrity contributes to spatial discrimination in older adults

Authors: *F. MARQUEZ[1], J. A. NOCHE[3], M. S. LARSON[3], D. DELISLE[3], E. MURRAY[3], L. MCMILLAN[3], M. WITBRACHT[2], S. SIRIVONG[2], J. GRILL[2], M. A. YASSA[3]
[1]Univ. of California Irvine Dept. of Neurobio. and Behavior, [2]Inst. for Memory Impairments and Neurolog. Disorders, Univ. of California Irvine, Irvine, CA; [3]Neurobio. and Behavior, Univ. of California Irvine Dept. of Neurobio. and Behavior, Irvine, CA

Abstract: Studies suggest that two neocortical systems interact with subcortical areas (including the hippocampus) to support memory for objects and memory for spatial navigation. The hippocampus is connected to other brain regions via two major limbic tracts: the fornix and the cingulum bundle, which includes the hippocampal cingulum and superior cingulum. In healthy adults (51.8 ± 18.9 years; MMSE: 29.02; RAVLT Delay: 11.52), significant relationships between chronological age and integrity of the hippocampal cingulum and fornix tracts have been described previously, and behavioral assays have shown a relationship between object discrimination and fornix integrity. While asymptomatic older adults have major deficits on object discrimination, they only show subtle deficits on the comparable spatial discrimination task when compared to young adults. If spatial discrimination is supported by hippocampal connections to a broader neocortical network, then deficits in spatial discrimination may be mediated by the integrity of limbic tracts. In this study, older adults (74.6 ± 7.5 years; MMSE: 27.94 ± 1.39 RAVLT Delay: 9.94 ± 4.46) underwent diffusion tensor imaging (2.2 mm nominal isotropic resolution) and completed the object and spatial mnemonic discrimination tasks. Behaviorally, we found a positive correlation between performance on RAVLT Delay and spatial discrimination (r^2=0.271, p=0.0054), but no relationship between performance on RAVLT Delay and object discrimination (r^2=0.002, p=0.80). Targeted tractography analyses revealed that hippocampal cingulum integrity (fractional anisotropy, mean diffusivity, and restricted diffusion) was significantly related to mnemonic discrimination for spatial memory, but not for object memory. These findings support the idea that deficits in spatial memory manifest due to hippocampal disconnection to neocortical systems via the hippocampal

cingulum. The results additionally suggest that the integrity of the hippocampal cingulum may be a biomarker that is associated with cognitive changes particularly related to spatial memory.

Disclosures: F. Marquez: None. **J.A. Noche:** None. **M.S. Larson:** None. **D. Delisle:** None. **E. Murray:** None. **L. McMillan:** None. **M. Witbracht:** None. **S. Sirivong:** None. **J. Grill:** None. **M.A. Yassa:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.21/III22

Topic: H.02. Human Cognition and Behavior

Support: RO1MH102392

Title: Structural integrity deficits of uncinate fasciculus predict medial temporal lobe activity during an emotional pattern separation task

Authors: *S. J. GRANGER[1], S. L. LEAL[2], E. A. MURRAY[3], M. A. YASSA[3]
[1]Neurobio. and Behavior, Univ. of California, Irvine, Coto De Caza, CA; [2]Univ. of California, Berkeley, Berkeley, CA; [3]Univ. of California Irvine, Irvine, CA

Abstract: The medial temporal lobe (MTL) is well known for its role in contributing to the formation of lasting memories. Specifically, the dentate gyrus (DG) and CA3 subfields of the hippocampus are thought to contribute to a neural computation known as Pattern Separation which the brain uses to distinguish between highly similar items (known as “lures”) during recall. One version of the paradigm designed to tax the pattern separation process is known as the Emotional Pattern Separation task and has been employed to study the effects of emotional discrimination. Although the MTL’s functional activity has begun to be categorized during these Pattern Separation tasks, the role of the prefrontal cortex (generally thought to exert top-down influence over cognitive processes) in regulating pattern separation processes is still relatively unclear. The prefrontal cortex is structurally connected to the anterior MTL through a dense white matter bundle known as the uncinate fasciculus (UF). Deficits of the UF have been implicated in those exhibiting depressive symptoms and larger structural integrity measurements have been shown to positively correlate with memory performance in tasks involving highly similar items. It is possible that the UF is highly involved in top-down influence in both emotional and non-emotional memory discrimination affecting MTL subfield activity. Thus, we hypothesize that deficits in UF integrity might predict aberrant DG/CA3 activity during emotional lure discrimination performance and poorer measures of lure discrimination. Using high resolution fMRI and “model-free” tractography methods from diffusion weighted imaging

we found that structural integrity deficits of the left UF are associated with increased activity of DG/CA3 in the left hemisphere only during the correct rejections of emotional and not neutral items. Further, increased DG/CA3 activity during correct discrimination of negative lure items was associated with poorer negative lure discrimination. Finally, using a causal mediation analysis, we provide evidence for a marginal effect of DG/CA3 activity mediating the relationship between UF integrity and lure discrimination for negative items. Past studies have suggested that hippocampal hyperexcitability may be an aberrant condition that predicts mild cognitive impairment and poor memory performance, here we suggest that hyperactivity of DG/CA3 mediates the relationship between deficits in structural top-down inhibitory control and poorer lure discrimination. A larger sample size will allow us to further investigate this intricately interconnected system between brain structure, function and memory performance.

Disclosures: S.J. Granger: None. **S.L. Leal:** None. **E.A. Murray:** None. **M.A. Yassa:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.22/III23

Topic: H.02. Human Cognition and Behavior

Support: NINDS T32NS45540
NIMH R01MH102392
NIA R21AG049220

Title: Gamma power in the human medial temporal lobe and prefrontal cortex predicts error and learning in a spatial memory task

Authors: *R. F. STEVENSON[1], J. T. JANECEK[2], J. ZHENG[3], L. MNATSAKANYAN[4], S. VADERA[5], R. T. KNIGHT[6], J. J. LIN[4], M. A. YASSA[2]
[2]Neurobio. and Behavior, [3]Biomed. Engin., [4]Neurol., [5]Neurolog. Surgery, [1]Univ. of California, Irvine, Irvine, CA; [6]Univ. of California Berkeley, Berkeley, CA

Abstract: The ability to learn novel associations is thought to depend on local processing within the medial temporal lobe (MTL) and prefrontal cortex (PFC) as well as functional interactions between these two regions. However, the ways in which the MTL and PFC contribute to associative learning in humans as well as the dynamics of MTL-PFC interactions remain poorly understood. We tested pre-surgical epilepsy patients with depth electrodes implanted in both the MTL and PFC using a spatial memory task in which subjects attempted to learn object-location associations over the course of three training blocks. During encoding, patients were shown objects at random locations along the circumference of an invisible circle. For each training

block, the same objects were shown at the top of the circle and patients used a dial to rotate the object to where it appeared during encoding. After patients finished placing each object, the object was shown in the correct location for one second as feedback. Following the three training blocks there was a final test during which no feedback was given. Angular error between the correct location and the indicated location was recorded as a continuous measure of performance. At retrieval, we found greater gamma (40-100 Hz) power in the MTL and PFC for more precise trials (less error). The opposite pattern of activity was observed at feedback, with greater MTL and PFC gamma power for less precise trials (more error). Increased MTL and PFC activity at feedback also predicted greater decreases in error from one training block to the next, indicating that these error signals are involved in updating memory representations or modifying incorrect associations during learning. Together, these results suggest possible mechanisms for the learning of object-location associations.

Disclosures: R.F. Stevenson: None. **J.T. Janecek:** None. **J. Zheng:** None. **L. Mnatsakanyan:** None. **S. Vadera:** None. **R.T. Knight:** None. **J.J. Lin:** None. **M.A. Yassa:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.23/III24

Topic: H.02. Human Cognition and Behavior

Support: NIA Grant R01AG053555
NIA Grant R21AG049220

Title: Interference resolution in memory: Beyond the medial temporal lobe

Authors: *C. CHWIESKO, M. A. YASSA
Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: The Object Mnemonic Discrimination Task (MDT-O) is a task designed to test pattern separation (the ability to minimize interference across similar stimuli in memory). Overcoming mnemonic interference in this task has been associated with the integrity of hippocampal Dentate Gyrus and CA3, which are hypothesized to be particularly critical in supporting pattern separation. In line with this hypothesis, the decline in performance observed in older subjects in the MDT-O has been linked to aging-related structural and functional changes in these areas.
However, aging is also known to affect the function of the Prefrontal Cortex (PFC). In addition, the PFC, in particular the Anterior Cingulate Cortex and the Dorsolateral Prefrontal Cortex, have been shown to play a critical role in interference resolution. This raises the question whether the

PFC could also contribute to the ability to overcome interference in the MDT-O.
The present study investigated this question by assessing the performance of young (n=21, mean age: 21.3 years) and old (n=34, mean age 74.2 years) subjects in the MDT-O and in the STROOP task (sensitive to PFC function in the context of interference resolution). More precisely, the STROOP task measures one's ability to inhibit cognitive interference. As previously reported, older subjects showed a significantly worse performance in mnemonic discrimination and in the STROOP task. More interestingly, the ability to mnemonically discriminate between similar stimuli in the MDT-O and the PFC related ability to inhibit cognitive interference in the STROOP task was significantly correlated. The observed correlation seems to be specifically related to inhibitory control processes of the PFC, as other measures of executive function did not correlate with mnemonic discrimination. Overall, these findings indicate that overcoming mnemonic interference in the MDT-O may not solely rely on pattern separation in the Hippocampus, but also potentially on interference resolution through inhibitory control mechanisms in the PFC.

Disclosures: C. Chwiesko: None. **M.A. Yassa:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.24/III25

Topic: H.02. Human Cognition and Behavior

Support: Grants-in-Aid for Young Scientists B (16K20930)
Global Initiative for Human High Performance (HHP) Research Project (1111501004)
KAKENHI Grants-in-Aid for Scientific Research on Innovative Areas entitled "Next generation exercise program for devel- oping motivation, body and mind performance (16H06405)

Title: Effect of a six-week mild exercise intervention on volume of the hippocampal dentate gyrus and CA3

Authors: *K. BYUN[1], K. SUWABE[1], K. HYODO[2], N. TUSTISON[3,4], M. A. YASSA[1,4], H. SOYA[1]
[1]Fac. of Hlth. and Sport Sci., Univ. of Tsukuba, Tsukuba-Shi, Japan; [2]Physical Fitness Res. Inst., Meiji Yasuda Life Fndn. of Hlth. and Welfare, Hachioji-shi, Japan; [3]Dept. of Radiology, Univ. of Virginia, Charlottesville, VA; [4]Ctr. for the Neurobio. of Learning and Memory, Dept. of Neurobio. and Behavior, Univ. of California, Irvine, Irvine, CA

Abstract: Age-related neurobiological changes are observed in the hippocampus in experimental model systems as well as in elderly humans. Although regular exercise is thought to counteract these age-related changes in hippocampal structure and function, there is very little work examining the impact of low-intensity exercise on hippocampal memory. This is an important avenue, as low-intensity or mild exercise is practically applicable to elderly with low fitness levels. Recently, there has been increasing evidence indicating that mild exercise in rodents activates hippocampal neuron and enhances adult neurogenesis especially in the dentate gyrus (DG), which plays a key role in hippocampal memory formation. However, the impact of a short term mild exercise intervention on human DG structure and function has not been previously evaluated. A total of 49 healthy old adults (mean age 66 ± 5.6; 6 males) took part in the baseline assessment of this study. We examined associations among age, aerobic fitness, and hippocampal subfield volumes (left and right DG/CA3, CA1, and subiculum). To assess individual maximal aerobic fitness (VO_{2peak}), participants performed a graded exercise test with a recumbent ergometer. From this sample, seventeen older adults participated in the intervention, which was implemented by a fitness trainer and met three times per week for 6 weeks. A high-resolution structural MRI scan using a T1-weighted 1mm isotropic MPRAGE sequence was collected before and after the exercise program for hippocampal subfield segmentation. Examining the baseline data, we found that both DG/CA3 volume and aerobic fitness level were negatively associated with age, as one might expect. However, DG/CA3 volume was positively correlated with baseline aerobic fitness level. We have previously shown that aerobic fitness is associated with DG-mediated pattern separation performance (Suwabe et al., 2017). Further, we found that mild exercise training was associated with increased volume of the left DG/CA3. To our knowledge, this is the first empirical evidence that even short term mild exercise can potentially increase DG/CA3 volume. Future work will examine how long lasting these effects may be and correlate volume increases to memory enhancement.

Disclosures: K. Byun: None. **K. Suwabe:** None. **K. Hyodo:** None. **N. Tustison:** None. **M.A. Yassa:** None. **H. Soya:** None.

Poster

694. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 694.25/III26

Topic: H.02. Human Cognition and Behavior

Title: Functional connectivity in a Down syndrome model of preclinical Alzheimer's disease

Authors: *N. DIPROSPERO[1], L. MCMILLAN[2], A. P. SMITH[2], M. S. LARSON[2], E. DORAN[3], I. T. LOTT[4], M. A. YASSA[2]

[2]Neurobio. and Behavior, [1]Univ. of California, Irvine, Irvine, CA; [4]Pediatrics, [3]UC Irvine Med. Ctr., Orange, CA

Abstract: Individuals with Down syndrome (DS) are at increased risk for developing Alzheimer's disease (AD) and have earlier symptom onset at an average age of 55, compared to age 80 in the general population, indicating that they may represent a model of early susceptibility for AD. The additional copy of chromosome 21 contributes to increased levels of amyloid precursor protein and subsequent accumulation of Aβ peptides beginning at age 40. Previous studies in individuals without DS have shown that both Aβ positive cognitively normal older adults and Aβ positive older adults with mild cognitive impairment (MCI) have altered functional connectivity in the medial temporal lobe (MTL) and the hubs of the default mode network (DMN), but few studies have investigated functional connectivity in individuals with DS over the age of 40. We hypothesize that the functional connectivity profile of older individuals with DS will look similar to that of Aβ positive cognitively normal older adults and Aβ positive MCI individuals. In the present study, we examine reduced connectivity within the MTL and the DMN, as well as reduced connectivity between the MTL and the DMN.

Disclosures: N. DiProspero: None. **L. McMillan:** None. **A.P. Smith:** None. **M.S. Larson:** None. **E. Doran:** None. **I.T. Lott:** None. **M.A. Yassa:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.01/III27

Topic: H.02. Human Cognition and Behavior

Support: Gu227/16-1
GE2777/2-1
An-2015-0044

Title: Neurite architecture of the planum temporale predicts neurophysiological processing of auditory speech

Authors: *P. FRIEDRICH[1], S. OCKLENBURG[1], C. FRAENZ[1], C. T. SCHLÜTER[1], C. BESTE[2], O. GUNTURKUN[1], E. GENC[1]
[1]Dept. of Biopsychology, Ruhr-University, Bochum, Germany; [2]Universitätsklinikum Carl Gustav Carus, Dresden, Germany

Abstract: The left-hemispheric advantage in speech perception is reflected in faster neurophysiological processing. Based on post-mortem data, it has been suggested that asymmetries in the organization of the intrinsic micro-circuitry of the posterior temporal lobe

may produce this leftward timing advantage. However, whether this hypothetical structure-function relationship exists in living human subjects has never been empirically validated.
To test this assumption, we used a diffusion MRI-based method called "neurite orientation dispersion and density imaging" (NODDI) to quantify micro-circuitry in terms of axon and dendrite complexity of the left and right planum temporale in 98 right-handed individuals. Furthermore, the cortical processing times of auditorily presented consonant-vowel syllables and white noise control stimuli were assessed via latencies of N1 event-related potentials in the EEG. We found that a higher density of dendrites and axons in the left planum temporale is associated with faster neurophysiological processing in the left hemisphere ($r = -.25$, $p < .05$), indicated by shorter N1 latencies. In contrast, N1 latencies after presentation of white noise were not associated with the planum temporale neurite architecture ($r = .01$, $p = .99$), indicating that the structure-function relationship is specific for speech-related stimuli.
Our results thus imply that a higher density and number of synaptic contacts in the left posterior temporal lobe increases temporal precision and decreases neurophysiological processing time during speech perception.

Disclosures: P. Friedrich: None. **S. Ocklenburg:** None. **C. Fraenz:** None. **C.T. Schlüter:** None. **C. Beste:** None. **O. Gunturkun:** None. **E. Genc:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.02/III28

Topic: H.02. Human Cognition and Behavior

Title: State-dependent TMS reveals the differential contribution of ATL and IPS in the representation of social and magnitude abstract concepts

Authors: *S. F. CAPPA[1], E. CATRICALÀ[1], F. CONCA[1], A. FERTONANI[3], S. FINAZZI[3], C. RODELLA[3], V. BORSA[2], C. MINIUSSI[4]
[1]IUSS, Pavia, Italy; [2]IUSS, Brescia, Italy; [3]IRCCS S. Giovanni di Dio, Brescia, Italy; [4]Univ. of Brescia; CIMeC, Univ. of Trento,, Brescia, Rovereto, Italy

Abstract: Introduction There is growing interest in understanding how abstract concepts are represented in our brains. While some authors support the idea that all concepts are stored in a single hub in the anterior temporal lobe (ATL), others propose distinct regions specialized for different types of abstract concepts. A role of social and magnitude dimensions in the representation of specific classes of abstract concepts has been reported (Troche et al., 2014). While social concepts have been associated to the superior ATL, the right intraparietal sulcus (rIPS) has been linked to numerical magnitude and to arithmetic concepts. We investigated the causal role of the right sATL and rIPS in representing social and magnitude concepts, using a

state-dependent transcranial magnetic stimulation (TMS)-priming paradigm in healthy subjects. Materials & Methods Eighteen subjects took part in the study. Fifty-six nouns, 28 social and 28 magnitude words matched for letter and syllable number, frequency, familiarity, imageability, valence, and mean priming effect (all p>.59), obtained from a pilot study, were employed. Priming to a category name (either "SOCIAL" or "QUANTITY") was used with the objective of modulating the initial activation state of each region prior to application of TMS and the presentation of the target stimulus. The experiment involves 56 congruent (SOCIAL-social target, QUANTITY-magnitude target) and 56 incongruent (SOCIAL-magnitude target, QUANTITY-social target) stimuli pairs, repeated for each site, namely the right sATL, the rIPS and the sham-control site (Vertex). Subjects were asked to indicate whether the target belonged to the quantity or social category. Results To investigate whether TMS interfered with the priming effect, the difference between congruent and incongruent trials found in the Vertex stimulation site was compared with that of the other two TMS conditions for each category separately. Pairwise comparisons revealed a abolition of the priming effect in rATL only for social words (p= .013), whereas in the rIPS the TMS effect was significant for both types of words (p <.05). Discussion Our results suggest that distinct brain regions are specialised for the processing of different types of abstract concepts. The rIPS is involved in magnitude concepts processing, in line with its role in the abstract numerical magnitude representation. Social concepts are represented in both right sATL and rIPS, in agreement with their respective role in social cognition and person-related knowledge (Mitchell & al., 2002).

Disclosures: S.F. Cappa: None. **E. Catricalà:** None. **F. Conca:** None. **A. Fertonani:** None. **S. Finazzi:** None. **C. Rodella:** None. **V. Borsa:** None. **C. Miniussi:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.03/III29

Topic: H.02. Human Cognition and Behavior

Support: ERC Grant 669820 (LKT)
BBSRC and MRC (CamCAN)

Title: Visual word recognition across the adult life span: A MEG study

Authors: M. KARADAG[1], C. WHITING[2], J. KLIMOVA[1], A. CLARKE[1], *L. K. TYLER[1], W. MARSLEN-WILSON[1]
[1]Univ. of Cambridge, Cambridge, United Kingdom; [2]Inst. of Neurosci. and Psychology, Univ. of Glasgow, Glasgow, United Kingdom

Abstract: Although some cognitive processes decline with age, spoken language comprehension remains unimpaired. Little is known, however, about how reading skills change over the adult lifespan, and no research has been conducted using spatiotemporally resolved imaging methods. A recent MEG study using the CamCAN cohort (a population-representative sample, age-range 18-88), found significant slowing with age in early visual responses to simple visual forms. Reading, however, involves a complex series of low- to high-level analysis processes, distributed over the brain, where an early stage of orthographic processing of letter strings is followed by morphemic analysis and by lexical access to specific word meanings. Previous MEG studies with young adults characterise a set of regions in occipital, temporal and frontal cortex where these processes are localised (Whiting et al., 2014). The current study, using CamCAN cohort MEG data, investigates the relative timing and the location of these processes in the aging brain, testing three groups of participants (Young (n=25, ages: 22-38), Middle (n=25, ages: 46-60) and Older (n=25, ages: 70-88).
Participants read silently 380 visual stimuli: simple words (e.g., *biscuit*), consonant strings (e.g., *hywc*), and morphologically complex words (*jumped, darkness*). MEG data were pre-processed and source localised using each subject's structural MRI scans. We first computed early visual evoked responses for each age-group in the early visual regions. Parallel responses for each age group were seen bilaterally in the occipital pole, with slight slowing for the older participants (~10 ms). We then tested for differences between words and consonant strings to detect the onset of orthographic processing across age groups. The Young group showed orthographic effects from 150 ms in bilateral posterior regions, similar in onset and location to the earlier Whiting et al result. The Older group showed major slowing (65 ms) in the onset of orthographic processing with only right hemisphere effects. Focusing on the temporal lobe ROIs where Whiting et al (2014) saw lexical effects, we computed lexical processing effects for each group using Representational Similarity Analysis. Consistent with the previous study, the Young group showed lexical effects in the posterior superior temporal gyrus from 370 ms, the Middle group showed similar but weaker effects, but the Older group showed no consistent effects at any temporal ROIs. Although CamCAN behavioural data shows similar reading proficiency across the adult lifespan, these spatiotemporally resolved data suggest significant age-related divergences in the neural systems involved.

Disclosures: M. Karadag: None. **C. Whiting:** None. **J. Klimova:** None. **A. Clarke:** None. **L.K. Tyler:** None. **W. Marslen-Wilson:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.04/III30

Topic: H.02. Human Cognition and Behavior

Support: MOST-106-2410-H-008-054
MOST-105-2410-H-008-054

Title: Brain connectivity was modulated by sentence difficulty as revealed by fMRI-ICA in Chinese relative clause

Authors: *K. XU[1], Y.-Y. HUANG[2], J.-R. DUANN[1]
[1]Inst. of Cognitive Neurosci., Natl. Central Univ., Taoyuan, Taiwan; [2]Natl. Central Univ., Taiyuan, Taiwan

Abstract: Introduction: Relative clause is one type of sentence with embedded structure among languages. Previous studies have revealed that the essential roles of the left superior temporal and frontal gyri (LSTG and LIFG), which might subserve reordering and storage of linguistic components, in processing relative clause in Indo-European languages. However, it is unclear whether or how these brain regions are functionally connected in a typologically different language, like Chinese. On the other hand, there is the preference between two main types of relative clause, that is, subject relative clause (SRC) and object relative clause (ORC). The preference for SRC over ORC has been clearly established in English and other head-initial languages, but whether the same preference is observed in Chinese is still on a heated debate. Furthermore, there are few studies elucidating the neural mechanism underlying such preference. **Hypothesis:** LIFG and LSTG was involved in processing Chinese Relative clause, similar with English studies. As the difficulty of Chinese relative clause changed, the effective connectivity between LIFG, especially subareas of LIFG, and LSTG would be different. **Method:** In the present mixed-trial fMRI study, the MRI image was acquired using a 3T scanner with a 64-channel whole-head coil. Then, the functional MRI data was processed using independent component analysis (ICA) method. Afterwards, task-related time series of different functional brain areas were further examined using GCA based on a multivariate autoregressive model. **Results:** LIFG and LSTG exhibited higher activation in processing more difficult Chinese subject relative clause (SRC) compared to Chinese object relative clause (ORC). Moreover, the similar neural networks but with different effective connectivity between brain areas were identified in reading SRC and ORC. Specifically, when comprehending more difficult Chinese SRC, the effective connectivity from BA44/45 to BA47 then extent to LSTG was found to be significant, while reading the simple ORC, only the connectivity from LSTG to BA 47 without the involvement of BA 44/45 was shown to be evident. **Discussion:** The present study offered hemodynamic evidence for Chinese ORC preference, particularly in the processing mechanisms that are supported by LIFG and LSTG, which was consistent with previous findings in English. Moreover, the result not only confirmed the specific roles of LIFG and LSTG involved in processing relative clause, which subserved reordering and storage, but also demonstrated how the brain connectivity was modulated by sentence difficulty.

Disclosures: K. Xu: None. **Y. Huang:** None. **J. Duann:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.05/III31

Topic: H.02. Human Cognition and Behavior

Support: NIH R03DC014045
NARSAD Young Investigator Grant to TP

Title: Functional dissociation of language and working memory revealed by pattern analysis of subject-specific conjunction maps

Authors: *T. L. SCOTT[1], T. K. PERRACHIONE[2]
[1]Grad. Program for Neurosci., [2]Speech, Language, and Hearing Sci., Boston Univ., Boston, MA

Abstract: Separable brain networks with opposing functional specificity are thought to support language and working memory (WM) (Fedorenko et al. 2010; 2012). A consistent exception to this functional dissociation has been observed in neuroimaging of verbal working memory (VWM) tasks, which appear to recruit regions belonging to both networks. Here, we compare and contrast activation in the brains of individual subjects evoked during functional magnetic resonance imaging (fMRI) of language, VWM, and spatial working memory (SWM) tasks. We use novel analysis techniques designed to assess overlap and pattern similarity between tasks without requiring strict correspondence of voxel-based anatomical alignment between subjects. WM tasks contrasted maintenance of long vs. short sequences of auditorily presented digits (VWM) or visual spatial locations (SWM) to identify voxels responsive to WM load in individual subjects. The language task contrasted listening to clips of speech vs. unintelligible degraded speech (Scott et al. 2017). We identified eight brain areas where significant activity overlaps between language and VWM in a majority (> 80%) of participants. Patterns of activity evoked by the two tasks were only weakly correlated (median $r = 0.12$) in these regions. Only three brain regions were identified as showing overlap between language and SWM, but there was virtually no correlation in the patterns of task-evoked activation in these regions (median $r = -0.05$). Overlapping activity between VWM and SWM was found in 16 regions, with highly correlated patterns of activity across these tasks in each region (median $r = 0.44$). Two regions, left posterior middle frontal gyrus / precentral gyrus and left planum temporale were found to have significant overlap in all three comparisons. Ultimately, although several areas show classical conjunction between language and VWM task activation, our fine-grained analyses reveal that the patterns of activity in these conjoint regions are in fact relatively dissimilar. Conversely, pattern analysis of the conjunctions between verbal and spatial WM reveal highly convergent activation patterns. These results suggest a degree of functional segregation between language and WM computations, even in commonly-activated brain areas.

Disclosures: T.L. Scott: None. **T.K. Perrachione:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.06/III32

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant RC2DA029475

Title: Behavior, sex, and the brain: Relationships with dyslexia risk gene DYX1C1

Authors: *A. J. KRAFNICK
Psychology, Dominican Univ., River Forest, IL

Abstract: Twin studies have shown genetics to contribute between 30% and 70% of the chance of developing dyslexia (Scerri & Schulte-Körne, 2010). Specific genes linked with increased risk of dyslexia diagnosis include genes involved in neuronal migration during development (Galaburda et al., 2006). One specific gene, *DYX1C1*, has been shown to interact with estrogen receptors (Tammimies et al., 2012), and could help explain findings of sex differences in the brain profile of dyslexia (e.g. Evans et al., 2014). Here, using data from the Pediatric, Imaging, Neurocognition, and Genetics (PING) study, effects of genotype and sex on reading and brain phenotypes were investigated in group of typically developing children and young adults. 1199 subjects from PING (average age 12 years, range 3-21 years; 581 F) with imaging and genetic data were included in this study. Average cortical thickness and total surface area (generated by PING using Freesurfer; Fischl, 2012) of five left hemisphere posterior regions involved in reading (superior temporal sulcus, superior temporal gyrus, inferior parietal lobule, supramarginal gyrus, and fusiform gyrus) were investigated for sex and genotype effects from two *DYX1C1* SNPs (rs685935 and rs3742404). Sex and genotype effects of reading and vocabulary behavioral measures were also investigated.Reading and vocabulary scores showed significant effects of genotype for both SNPs (all p<0.05), and vocabulary scores showed a significant effect of sex in both models (p<0.05; higher scores in males). No genotype x sex interactions were observed. For average cortical thickness, no effects of genotype or genotype x sex interactions were found, but supramarginal gyrus showed a sex effect in both models (both p<0.05; thicker cortex in females). For surface area (controlling for total LH surface area), rs3742404 showed significant effects of genotype in superior temporal sulcus, inferior parietal lobule, and superior temporal gyrus (all p<0.05; AA > AC and CC). For surface area and rs685935, main effects of sex were observed for fusiform gyrus and supramarginal gyrus (both p<0.05; larger surface area in males) and a genotype x sex interaction was observed in superior temporal sulcus (p<0.05; virtually no difference amongst females, but larger surface area for GG compared to GA and AA in males). No genotype effects were observed for

rs685935 on surface area.These results provide evidence for sex and genotype effects for dyslexia risk gene *DYX1C1* related to reading ability. Differences in genotype effect by sex may help explain the different anatomical profiles of dyslexia observed at the volumetric level (e.g. Evans et al, 2014).

Disclosures: A.J. Krafnick: None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.07/III33

Topic: H.02. Human Cognition and Behavior

Support: NIH P50MH106435
S10OD020039
Kent and Liz Dauten
Ellison Foundation
WT103980MA

Title: Intrinsic connectivity within individuals reveals a distributed left-lateralized network that is language-responsive

Authors: *R. M. BRAGA[1,2], L. M. DINICOLA[1], K. R. VAN DIJK[3], J. R. POLIMENI[4], R. L. BUCKNER[1,3]
[1]Harvard Univ., Cambridge, MA; [2]Imperial Col. London, London, United Kingdom; [3]Massachusetts Gen. Hosp., Charlestown, MA; [4]Martinos Ctr. Biomed Imaging, MGH/Harvard Med. Sch., Charlestown, MA

Abstract: Group-averaged network estimation based on intrinsic functional connectivity (FC) often fails to delineate a left-lateralized network that is a clear candidate for supporting language function (but see Hacker et al., 2013 for an interesting exception). This has remained a puzzle because of the noted specialization for language. FC analysis of repeatedly scanned individuals has recently revealed that distinct, closely juxtaposed and interdigitated networks can be observed within canonical group-defined networks such as the default network (DN) and frontoparietal control network (FPN; Braga & Buckner, 2017). These networks were called DN-A, DN-B, FPN-A and FPN-B for convenience. A possibility is that blurring across individuals may obscure detection of a distinct, language-specialized network. Here, we explored the functional anatomy of individuals to determine whether a distinct candidate language network exists. Extensive resting-state data (>56 mins acquired at 3T, 2.4mm, 1.00s TR) were collected from each of 10 individuals, along with 40 mins of a language localizer task (Fedorenko et al., 2010). Data were registered to a subject-specific target and resampled to 1mm isotropic

resolution and smoothed at 2mm FWHM (yielding over 1.3TB of data per subject). Individual surface vertices were selected from the prefrontal cortex and used as seeds for the FC analysis. The resulting FC patterns identified distinct distributed networks. A putative language network within individuals was found consistently that is distinct from (but closely neighboring) other distributed association networks, particularly DN-B, FPN-A and FPN-B. This language network follows the broad distributed motif of other association networks (prefrontal, temporal, midcingulate and dorsomedial prefrontal cortices) but notably is absent a prominent posteromedial component. Fine-grained anatomical details of the distinct networks were explored in 3 subjects at high spatial resolution (24 mins acquired at 7T, 1.35mm, 1.49s TR). The language network could be identified in the volume with distributed components localized to the cortical ribbon that were distinguishable from adjacent networks on closely juxtaposed portions of the cortex. Finally, this distributed network overlaps with regions showing increased activation during a language localizer task, and its functional specificity forms part of ongoing investigation. Our results identify a clear candidate for a left-lateralized language network that is missed when data are averaged across subjects.

Disclosures: R.M. Braga: None. **L.M. DiNicola:** None. **K.R. Van Dijk:** None. **J.R. Polimeni:** None. **R.L. Buckner:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.08/III34

Topic: H.02. Human Cognition and Behavior

Title: Effects of the specific rehabilitation of defecit and pragmatic typo in patients with aphasia

Authors: *J. C. GALICIA, SR[1], M. A. MACÍAS[2], T. J. VILLASEÑOR[2], M. E. JIMÉNEZ[2], E. R. VILLUENDAS[3]
[2]Neurociencias, [1]Univ. de Guadalajara, Guadalajara, Mexico; [3]Facultad de Psicología Posgrado, Univ. Michoacána de San Nicolás de Hidalgo, Morelia, Mexico

Abstract: Introduction. Two approaches in rehabilitation of aphasia favorable results: the traditional or specific treatment of the deficit TED (which addresses the recovery of a particular linguistic function) and pragmatic or functional therapy TPF (aimed at improving communication skills). **Objective.** To compare the effects of TED and TPF in patients with aphasia and their language skills and communication. **Method.** 12 adults patients (66.7% W 33.3% M) with aphasia (9 Broca, 2 Wernicke and 1 Global) secondary to EVC, all preferably manually right, selected by convenience, crossover design (ABAB) single case, with two intervention groups (1 and 2) which includes two types of treatment five evaluation periods. Instruments: The evaluation periods were performed with the Boston Test for the Diagnosis of

Aphasia (TBDA) and the Protocol for the Evaluation of Communication of Montreal (MEC). Procedure: The rehabilitation program consists of two different treatment techniques, with 20 sessions of 1 hour, divided into four periods of treatment according to the intervention group. Evaluations were presented before and after each treatment period. **Results.** Visual analysis of the data showed in both treatment groups an upward shift in the expressive components (CEL), Listening (CCAL) and language proficiency rate (ICL). Also in the pragmatic tasks of conversational speech (DC), the interpretation of speech acts (IAH) and interpretation of metaphors (IM). Statistically significant differences by type of treatment in improving some language skills (ICL) and communication (DC) patients, after 20 treatment sessions were found. **Conclusions.** The results suggest that patients improved their language skills and communication are similar in both intervention groups, but by type of treatment differences. It is possible that increased communication skills attributable to TED results from the combination of specific exercises with words or family prayers used by patients premorbid form.

Disclosures: J.C. Galicia: None. **M.A. Macías:** None. **T.J. Villaseñor:** None. **M.E. Jiménez:** None. **E.R. Villuendas:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.09/III35

Topic: H.02. Human Cognition and Behavior

Title: The neural representation of number-noun phrases: An ECoG study

Authors: *V. C. CARUSO[1], G. B. COGAN[2], J. M. PEARSON, 27705[3], T. OVERATH[3], M. M. HAGLUND, 27705[3], S. R. SINHA, 27705[3], C. MUH, 27705[3], J. M. GROH[3]
[1]Ctr. For Cognitive Neurosci., [2]Dept. of Neurosurg., [3]Duke Univ., Durham, NC

Abstract: Speech entails the combination of words into structured phrases and sentences. Thus, a first essential step in understanding how speech meaning is encoded in the brain is to determine the neural responses of words uttered in combination. We focused on two-word spoken phrases consisting of a number followed by a concrete noun (such as “two books”). We recorded ECoG data from 7 participants undergoing pre-surgical monitoring for pharmacologically resistant epilepsy. In particular, we took an approach similar to single cell electrophysiology and tested whether the response to the noun is modulated (e.g. monotonically or in a tuned fashion) by the numerical quantity indicated by the preceding number. We recorded ECoG data while participants actively listen to two-word number-noun phrases (‘two’, ‘three’, ‘four’, ‘eight’, ‘ten’, and ‘book’,’chairs’,’dogs’). We quantified the neural response as the magnitude of the ECoG signal in the high gamma range (70 to 150Hz), because this has been proven to correlate strongly with the local neuronal population spiking activity. We report here preliminary data

from two subjects. We found that in the majority of the sound-responsive channels, the high gamma response during the second word was significantly modulated by the preceding number, as indicated in a two-way ANOVA by either a main effect of number or an interaction. This was still true in sites for which the activity during the number presentation and the delay time between the words was not modulated by the number. More data are needed to establish whether the trend is significant, determine the exact shape of the interaction and its time course, and test whether there is a spatial segregation between sites that show interaction vs. main effect of number. Investigating the neural representation of short phrases consisting of a limited number of stimuli provides a useful bridge between the tuning curve approach of single unit auditory neurophysiology and the higher level approaches of language studies.

Disclosures: G.B. Cogan: None. **J.M. Pearson:** None. **T. Overath:** None. **M.M. Haglund:** None. **S.R. Sinha:** None. **C. Muh:** None. **J.M. Groh:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.10/III36

Topic: H.02. Human Cognition and Behavior

Support: SFI Grant CDA/15/3316
IRC Postgraduate Scholarship

Title: EEG correlates of natural, narrative speech processing at the level of phrases

Authors: J. HOOGENDOORN[1], M. P. BRODERICK[2], G. M. DI LIBERTO[3], *E. C. LALOR[4]
[2]Neural Engin., [1]Trinity Col. Dublin, Dublin, Ireland; [3]DEC, École Normale Supérieure, Paris, France; [4]Univ. of Rochester, Rochester, NY

Abstract: One fascinating aspect of language is recursion**;** technically, you could keep adding in phrases to create a never-ending sentence. Although humans do tend to finish their sentence eventually, listeners are left with the task to identify which words combine into a phrase. Recent research has begun to provide evidence for neural signals that may reflect this process. In particular, high gamma power activity from intracranial recordings has been shown to monotonically increase with each additional word in a phrase, and to drop at phrase ending. And EEG alpha power has been suggested to reflect syntactic processing, with reports of a power increase within a clause, followed by a drop in power at the end of the clause. This suggests that there is a build-up of neural activity during a phrase, or during a clause, relating to a hierarchical parsing of syntactic structure. While these results are compelling, they have typically been shown only in the context of experiments involving presentation of isolated sentences. Indeed even these sentences often have very specific and predictable structures. Thus, it remains

possible that the reported neural signatures of phrasal processing may be somewhat confounded by attentional fluctuations based on the constrained and predictable nature of the stimuli. Here, we aim to explore if some of these neural measures still reflect syntactic processing while subjects listen to more natural, narrative speech. Ten subjects listened to a ninety-minute segment of an audiobook while their EEG was being recorded using 128 channels. Alpha power (between 8 and 12Hz) was extracted from the EEG signal. We derived a measure that models the build-up over phrases by identifying the start and end of the verb phrases within our speech stimuli, and modelled this build-up over a verb phrase as a saw tooth wave. Using a stimulus-response mapping technique known as the Temporal Response Function (TRF), we fit a model based on this quantity and the alpha power of the recorded EEG. We use this model to predict EEG in a leave-one-out cross validation analysis. We found significant prediction accuracies over left temporal channels, which were consistent across subjects. This indicates that EEG may track the syntactic build up over the length of a phrase. Having such a measure would allow for studying syntactic processing under more naturalistic conditions of natural, narrative, continuous speech, using EEG.

Disclosures: J. Hoogendoorn: None. **M.P. Broderick:** None. **G.M. Di Liberto:** None. **E.C. Lalor:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.11/III37

Topic: H.02. Human Cognition and Behavior

Title: Performance to verbal learning and verbal semantic predict based on resting state neural oscillations pattern

Authors: *V. OSWALD[1], Y. ZEROUALI[3], A. BOULET-CRAIG[4], P. JOLICOEUR[2], S. LIPPÉ[3], K. JERBI[2], P. ROBAEY[2]
[1]Univ. de Montréal, Montreal, QC, Canada; [2]Univ. de Montréal, Montréal, QC, Canada; [3]Univ. de Montreal, Montréal, QC, Canada; [4]Univeristé de Montreal, Montréal, QC, Canada

Abstract: Objective: In this study, we used resting state MEG (and not a task paradigm) to explore neural oscillations patterns correlated with the performance in a standardized verbal learning test. **Participants and methods**: We recorded 5-min eyes-open resting-state MEG data and administered the California Verbal Learning Test-II (CVLT-II) in 28 healthy subjects. In the CVLT-II the subject was asked to recall words from a list read aloud over five learning trials (List A), then from another List B presented once. A free-recall of List A was tested immediately and again after 20 min. A T1-weighted MRI images was used to generate a cortical surface model. Forward modeling of magnetic field activity was performed. We calculated means of

Power Spectrum Density for different frequency bands (delta, 1-4Hz; theta, 4-8Hz; alpha, 8-13Hz; beta, 13-30-Hz; gamma, 30-120Hz) and correlated normalized MEG power in each frequency band with the performance in the CVLT-II across trials, and trial by trial. In order to control multiple comparisons, we used a non-parametric cluster mass approach. **Results:** Based on the sequential detection of clusters for each trial, we identified three sets of correlations between CVLT performance and (1) auditory associative areas for the gamma band, (2) auditory associative and premotor areas for lower frequencies (mainly alpha and beta), (3) auditory associative and parietal areas across all frequencies. The first type of correlation clusters was mostly detected during List A trials 2 to 4, the interference List B trial, and the long-delay free recall trial. The second type was observed in trial 3 of List A, and in the short- and long-delay free recall trials. Finally, the third type was detected in trials 3 and 4 of List A. **Conclusions:** Resting state MEG can identify different processes involved in verbal learning, including semantic processing in the auditory associative areas and subvocal rehearsal distributed between the parietal and the premotor areas.

Disclosures: V. Oswald: None. **Y. Zerouali:** None. **A. Boulet-craig:** None. **P. Jolicoeur:** None. **S. Lippé:** None. **K. Jerbi:** None. **P. Robaey:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.12/III38

Topic: H.02. Human Cognition and Behavior

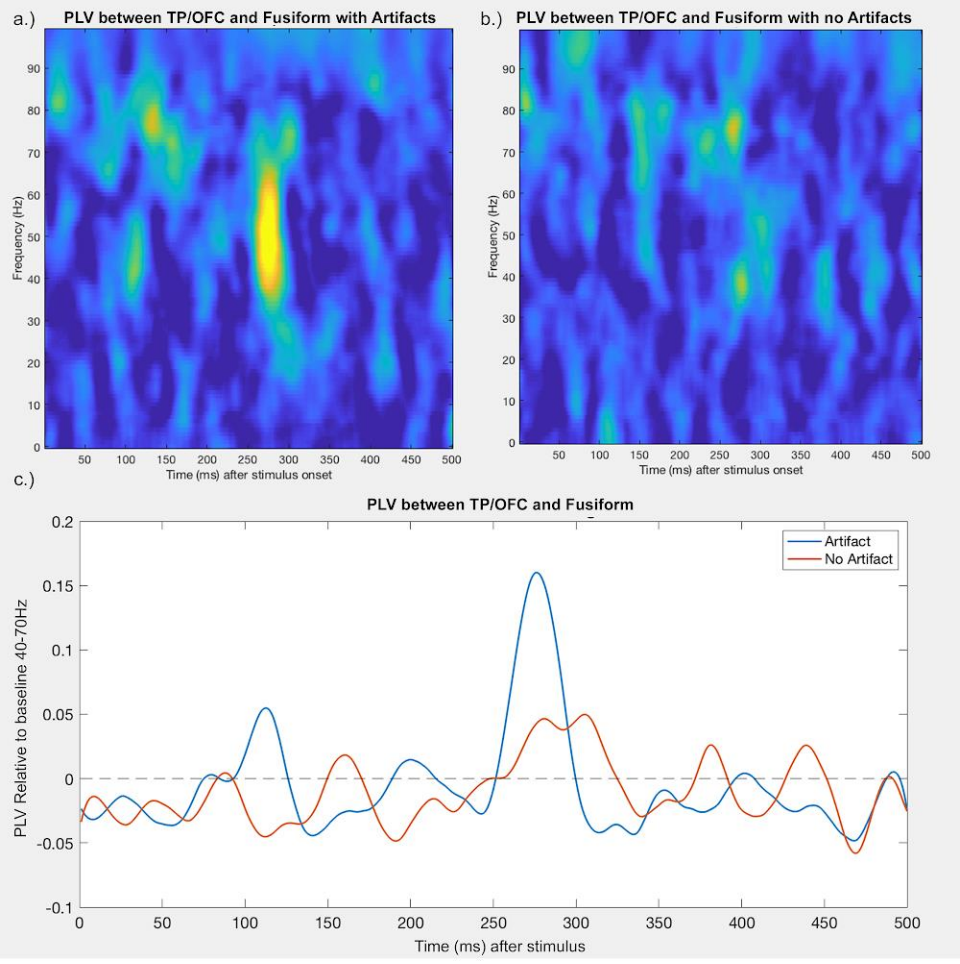
Support: NIH Grant DC014589

Title: Saccadic corruption of the top-down hypothesis for visual processing

Authors: *A. CURTIS[1], C. M. KADIPASAOGLU[2], K. FORSETH[4], N. TANDON[3]
[1]Rice Univ., Houston, TX; [2]Neurosurg., [3]Neurolog. Surgery, Univ. of Texas Med. Sch. at Houston, Houston, TX; [4]UT Hlth. Sci. Ctr. In Houston, Houston, TX

Abstract: Top-down visual object recognition in the orbitofrontal cortex (OFC) has been proposed to drive rapid processing of simple images in higher-level visual regions. Event-related long-range connectivity between OFC and fusiform, quantified with phase locking value (PLV) in the low gamma band (40 - 80 Hz), has been argued to constitute crucial evidence for this perspective. However, PLV in the gamma band can be contaminated by cranial and optical muscle artifacts in EEG recordings. Intracranial electrodes, including both surface grid electrodes (n = 467, 3 patients) and penetrating stereotactic depth electrodes (n = 547, 3 patients), were implanted for electrocorticographic (ECoG) pre-surgical evaluation of epilepsy. Furthermore, each of these patients was monitored with concurrent extracranial electrodes.

Patients completed a picture naming task in which they quickly and accurately articulated common object names. In this task, a third of the visual stimuli were rendered incoherent and patients responded with “scrambled.” We leverage this unique opportunity with paired intra- and extracranial EEG recordings of an essential language task to isolate the influence of non-neural signals (e.g. saccadic eye movements) on a prominent connectivity measure - PLV.Using non-parametric cluster based time-frequency statistics, we find that trials lacking saccade artifact in extracranial EEG also lack the corresponding low gamma band PLV increase (200 - 300 ms post-stimulus) in ECOG. We observed this same dissociation in the response to both coherent and scrambled pictures. Therefore, we demonstrate that the well-characterized saccadic spike potential can induce artificial PLV in EEG, which can sometimes be mistaken for neuronal activity in the low gamma band.The confounds introduced by saccadic spike potentials confounds crucial evidence for early top-down modulation of visual object recognition. Our findings help identify and characterize the saccadic artifact in ECoG experiments as well as differentiate it from true functional connectivity between cortical regions.



Disclosures: A. Curtis: None. **C.M. Kadipasaoglu:** None. **K. Forseth:** None. **N. Tandon:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

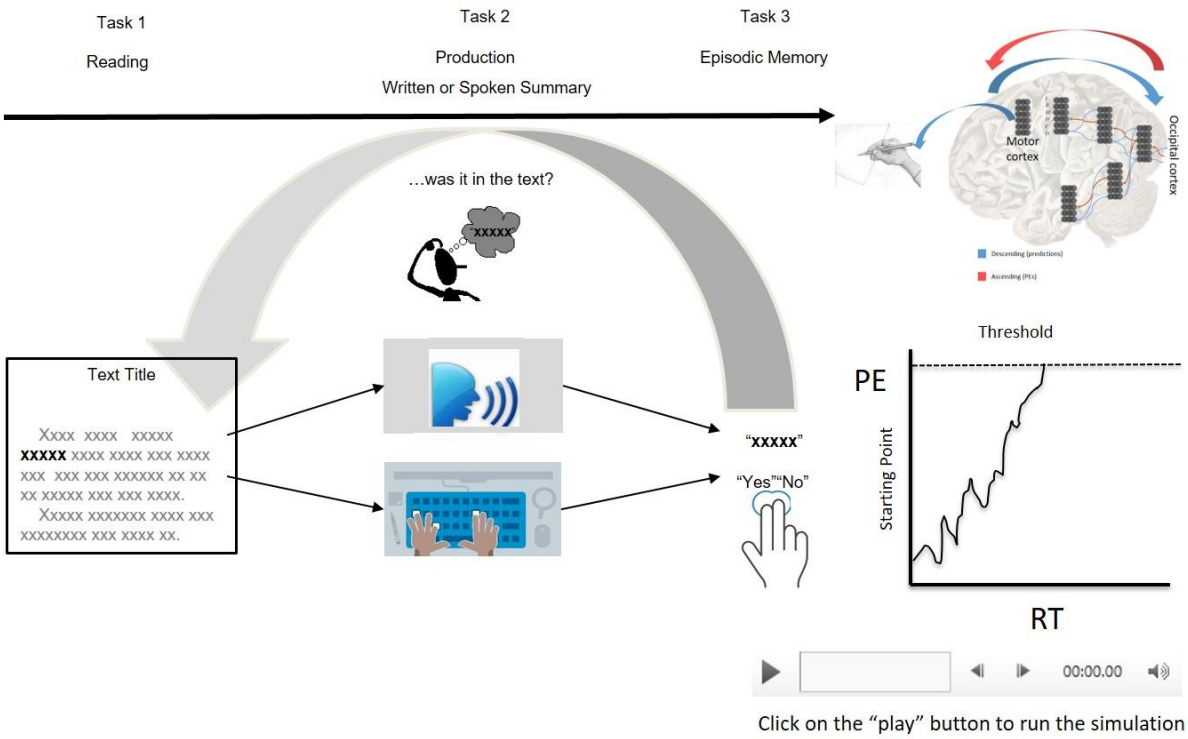
Program #/Poster #: 695.13/III39

Topic: H.02. Human Cognition and Behavior

Title: Evidence-accumulation models confirm the epistemic property of writing: A predictive coding and active inference study of writing to learn

Authors: A. M. SILVA[1], *R. LIMONGI[2]
[1]Sch. of Pedagogy, Pontifical Catholic Univ. of Valparaíso, Valparaíso, Chile; [2]INACAP Online, Technological Univ. of Chile, Santiago, Chile

Abstract: Writing plays a prominent role in both academic achievement and professional success because it allows to gain information, reduce uncertainty, and boost curiosity. This is, writing has an epistemic property. It is uncontested that writing enhances learning. However, what neural mechanisms underlie the learning effects of writing and how we could measure such effects are open questions. This paper proposes a new (Bayesian-brain) theoretical perspective about how writing affects learning and cognition: the predictive coding and active inference approach. Furthermore, it proposes an experimental task and a data analysis strategy to disambiguate the predictions of the dominant cognitive-psychology perspective of written composition and the emergent Bayesian perspective. In a simple experimental paradigm, participants read short passages, wrote or spoke a summary, and performed an episodic-memory recognition task. Reaction time of correct responses was shorter in the written condition than in the spoken condition. Furthermore, evidence-accumulation models revealed that writing optimized the prior beliefs that participants deployed when they summarized texts. Visual dynamic simulations of the competing evidence accumulation models show how a higher starting point value leads to a faster evidence accumulation towards the decision threshold. These findings support a Bayesian theory of brain function that regards epistemic writing as a specific case of active inference. Moreover, the results show a remarkable correspondence between the phenomenological notion of epistemic writing stated in the educational, linguistic, and psychology-of-writing fields and the neurocomputational formulations of predictive coding and active inference. Finally, the dynamic simulations provide tools for a visual and heuristic understanding of the complex neural process that underlies the effect of writing on memory.



Disclosures: A.M. Silva: None. **R. Limongi:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.14/III40

Topic: H.02. Human Cognition and Behavior

Support: Small Research Grant, Office of Research Support and International Affairs, Gallaudet University
National Science Foundation (SBE-1041725)

Title: Functional connectivity in the language network in response to syntactic complexity and acoustic degradation: A functional near-infrared spectroscopy study

Authors: *B. E. WHITE, C. LANGDON
PhD in Educational Neurosci. (PEN) Program, Gallaudet Univ., Washington, DC

Abstract: INTRODUCTION: Behavioral and neuroimaging research suggests that processing degraded acoustic information creates a cascading effect on the mechanisms underlying speech comprehension (Peelle, 2018). Here, using a plausibility judgment task and functional near-

infrared spectroscopy (fNIRS), we aim to dissociate motivated listening and its modulation of language processing in response to increased demands on executive functioning. Hypotheses. H1: Compared to simple, clear speech, the processing of complex and degraded speech increases demands on domain-general cognitive resources. P1: The functional connectivity between the posterior superior temporal gyrus (pSTG) and areas in the frontal and right temporal lobes will be stronger for more difficult speech. H2: Alternatively, the processing of complex and degraded speech increases demands on language networks primarily in the left temporal regions. P2: Functional connectivity will be stronger between the left pSTG and other left hemisphere language areas for more difficult speech. METHODOLOGY: Participants. Monolingual, English-speaking adult participants (N=4; ages 24-37) with clinically-defined typical hearing. Procedures. Participants complete a battery of language and cognitive assessments. The fNIRS task presents participants with 192 sentences for a plausibility judgment task. The sentences vary linguistically (i.e., simple subject-relative and complex object-relative clause structures) and acoustically (i.e., clear speech and 8-channel, noise-vocoded speech). RESULTS: Using the left pSTG as a seed region for functional connectivity analysis, we observed (1) stronger left inferior frontal gyrus (LIFG) and left anterior middle frontal gyrus (aMFG) connectivity in syntactically simple and noise-vocoded speech, (2) reduced overall connectivity for syntactically complex compared to syntactically simple grammar for both speech conditions, and (3) stronger LIFG, but weaker right hemisphere connectivity, for syntactically complex and noise-vocoded speech. CONCLUSION: While the syntactic complexity condition fails to indicate support for either hypothesis, functional connectivity with the left pSTG is distinctly modulated by acoustic degradation and indicates support for the hypothesis that increased demands are placed on attentional resources (H1).

Disclosures: B.E. White: A. Employment/Salary (full or part-time):; Gallaudet University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Gallaudet University. **C. Langdon:** A. Employment/Salary (full or part-time):; Gallaudet University.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.15/III41

Topic: H.02. Human Cognition and Behavior

Support: CONACYT CVU 621367
Fronteras de la Ciencia 2015 No.225

Title: In search of the cognitive abilities required for comprenhension of indirect request in Spanish speking young adults

Authors: *G. L. LICEA HAQUET[1], M. GIORDANO[2]
[1]Inst. De Neurobiología UNAM, Queretaro, Mexico; [2]Inst. de Neurobiología UNAM, Queretaro, Mexico

Abstract: Even though language allows us to say exactly what we mean, we often use language to say things indirectly, in those instances verbal comprehension represents only the starting point for an inferential process that results in the attribution of speaker´s meaning that involves recognition of speaker´s intentions. An indirect request is a common form of nonliteral language that can be understood either as literal, or as figurative requests for an action to be carried out. For example, the utterance "Can you open the door?" can be interpreted as an indirect request for the door to be opened. Or, taken literally, as "Are you physically able to open the door?"(Sperber & Wilson, 2002). There are different theories about how listeners identify speaker´s meaning, some studies suggest that listeners first compute the literal meaning, and if it is inappropriate to the context they infer the speaker's communicative intention. In contrast, other studies indicate that indirect requests are processed early on, even before the end of the sentence is heard (Coulson & Lovett, 2010). Based on empirical studies of populations suffering from various pathologies, it has been proposed that the recognition of the speaker´s intentions requires the integrity of other cognitive process such as executive functions and theory of mind, however, there are few studies in healthy controls. The aim of this work was to study the relation between the comprehension of indirect request and executive functions and theory of mind in a neurologically intact sample of native Spanish speakers. We translated and adapted to Spanish the stimuli used by van Ackeren, et. al.(2012), One hundred images and sentences were selected to design a decision task which evaluated indirect request identification using PsychoPy (Pierce, 2008). The participants (n=20, 21-35 years old) were indicated to see the images and read the sentences and indicated if they thought that somebody was making a request. The task was designed with two SOAs of 0.5 and 1.5 seconds to explore if the process is automatic or requires an inferential process. Participants also answered a psychometric battery that included executive functions and theory of mind tests. We found that participants showed worse performance in indirect requests than control trials, both with short and long SOAs. Only response time on a general cognitive ability task, explained the variance in reaction time for indirect requests. The behavioral tasks are currently being adapted to be used during acquisition of structural and functional images to determine the neural correlate of indirect request identification.

Disclosures: G.L. Licea Haquet: None. **M. Giordano:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.16/III42

Topic: H.02. Human Cognition and Behavior

Support: Fronteras de la ciencia, 2015, No. 225

Title: Differential involvement of the left and right hemispheres on the processing of verbs and pseudo-words

Authors: G. L. LICEA HAQUET[1], M. GIORDANO[1], *A. REYES AGUILAR[3,2], B. I. ARCE LÓPEZ[2]
[1]Univ. Nacional Autónoma de México, Querétaro, Qro., Mexico; [2]Neurosci., Univ. Nacional Autónoma de México, Mexico City, Mexico; [3]Inst. of Neurobio., Univ. Nacional Autonoma de Mexico, Queretaro, Mexico

Abstract: Language “comprehension” requires pre-lexical, and lexical-semantic processing. The neurobiological substrate in charge of these processes, according to the dual stream model, involves two networks with a common origin, the sensory/phonological system in the temporal and occipital cortices. According to this view, the dorsal stream would be connected to the motor-articulatory systems in the left frontal regions, while the ventral stream would connect to the conceptual-semantic systems in the ventral temporal cortex bilaterally. Verbs are a class of words that express action, occurrence, or mode of being. We were interested in evaluating the functional dissociation between pre-lexical and lexical-semantic processing of pseudowords and verbs, and their relation with language skills using functional magnetic resonance imaging (fMRI). We selected 112 verbs based on their psycholinguistic properties according to linguistics corpora. After validation of the stimuli in a behavioral study, we included three categories in the fMRI study: symbols, pseudo-words, and verbs in a one-back detection task. Twenty-four right-handed, young participants, gave written informed consent. Participants were scanned in a 3T GE MR750 scanner, and were requested to complete the vocabulary subtest of the WAIS, and verbal fluency tasks outside the scanner. Our results indicated that, in comparison to symbols, verbs recruited bilateral parietal, temporal and frontal regions, while pseudo-words showed involvement of the left hemisphere language network. Finally, verbs in contrast to pseudo-words, recruited right temporal and frontal areas. Region of interest analysis showed that vocabulary and verbal fluency performance was negatively correlated with the hemodynamic response in the left brain areas in the contrast verbs versus all other stimuli categories, and positively correlated with the hemodynamic response in the right posterior temporal region in the contrast pseudo-words vs symbols. These results suggest that pre-lexical processing evoked by pseudo-words, is lateralized to the left, and could reflect the attempt of the motor-articulatory system to recognize the stream

of letters. While lexical-semantic processing recruited bilateral fronto-parieto-temporal regions. Language proficiency, as measured by vocabulary and fluency tests, was related to less involvement of the left lexical-semantic system for verbs, and more involvement of the right motor-articulatory system for pseudo-words.

Disclosures: G.L. Licea Haquet: None. **M. Giordano:** None. **A. Reyes Aguilar:** None. **B.I. Arce López:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.17/III43

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DC009659

Title: Semantic and phonological errors described by a hierarchical computational model of speech production

Authors: M. TOPALIDOU[1], E. NEFTCI[1], *G. S. HICKOK[2]
[1]Univ. of California Irvine, Irvine, CA; [2]Univ. California, Irvine, CA

Abstract: Dell et al. (1997) implemented a hierarchical model of three layers (semantic, lexical, and phonological) to explain semantic and phonological speech errors for aphasic patients. Through a series of papers, Dell and his colleagues identify the strength of the connections between the units of the semantic and lexical, and the lexical and phonological layers as the main element for the variety of errors in aphasic patients during picture naming experiments (Foygel and Dell, 2000). Later, Walker and Hickok (2015) based also on the Hierarchical State Feedback theory (Hickok et al., 2011), extended the model by dividing the phonological layer to auditory and motor, to explain better conduction aphasia. However, none of the models include a internal feedback mechanism at the phonological level that can detect and correct phonological selection errors prior to overt speech output (Hickok, 2012). Our goal was to implement a mechanism that can achieve internal speech error detection and correction during multi-syllables production. We used the architecture proposed as one level in the Hierarchical State Feedback Control (HSFC) model as described in Hickok, et al. (2011) with the addition of a semantic level as in Dell's model. The network comprises five structures: semantic, lexical, auditory-phonological, motor-phonological, and auditory-motor intermediary (Spt) levels. The lexical level is bidirectionally connected to the semantic, auditory and motor levels. The two latter structures are connected to each other also via the Spt auditory-motor interface level. Our model does not separate the sequence of the phonemes in onsets, vowels and codas as in previous models. The needed information of the sequence is provided by the connections weights between the word (in the

lexical level) and the phonemes (in auditory and motor level). Internal error correction is hypothesized to occur via auditory-motor interaction in cases where the motor plan does not match the lexical and auditory targets (Hickok, 2012). Analysis of network behavior showed that motor errors can be corrected by Spt driving the correction. Another outcome of the analysis was that word sharing of semantic features is enough to produce occasional/rare semantic errors. One prediction of the model based on these results is that the more semantic features two word share, the more likely is the wrong word to be produced. On the contrary, the phonological errors should be less frequent, because of the internal feedback mechanism at the phonological level; a component that the semantic level lacks.

Disclosures: M. Topalidou: None. **E. Neftci:** None. **G.S. Hickok:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.18/III44

Topic: H.02. Human Cognition and Behavior

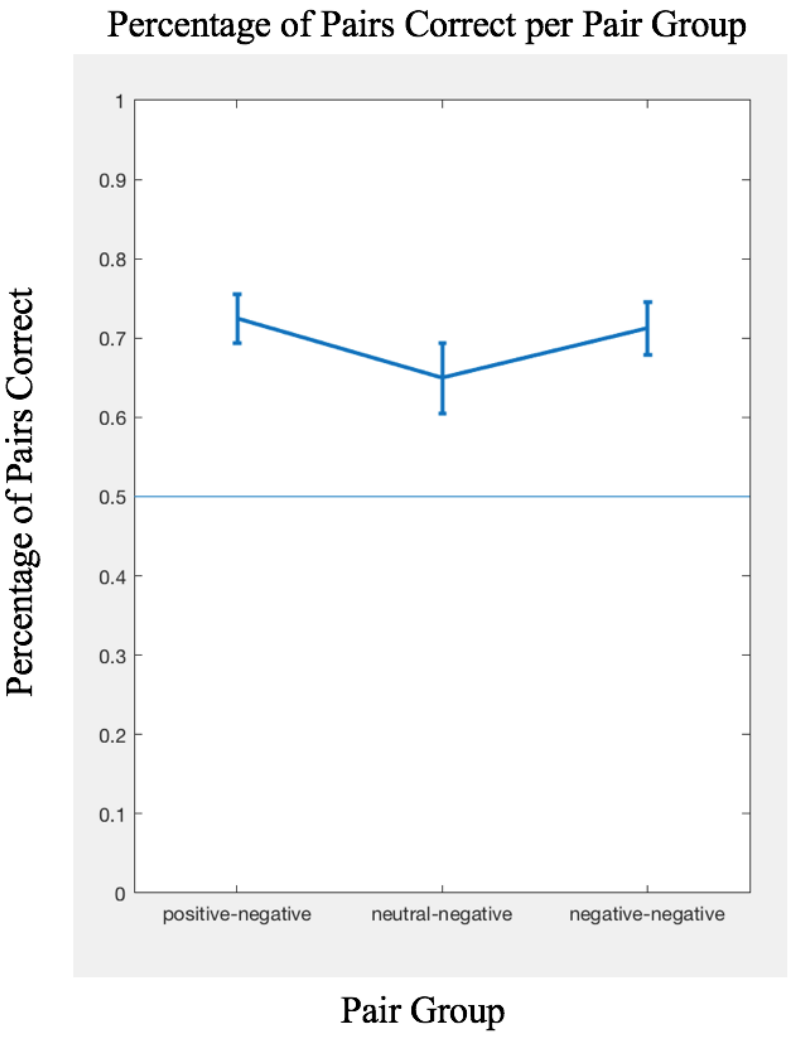
Support: Gift Donations to the Center of Brain and Cognition

Title: Subtle emotional distinctions in primate vocalizations (chimps and vervets) can be recognized by naive humans; evolution of proto-language in left hemisphere and musical scales (ragas) in the right hemisphere - mediated by a primordial emotional language of intonation and prosody via ultra normal peak-shift

Authors: *V. S. RAMACHANDRAN, S. KANDALAFT, K. VAYYALA, C. CHUNHARAS, Z. MARCUS
UCSD, La Jolla, CA

Abstract: Two great enigmas are the evolution of music and of language; both of which require retracing the sequence of steps through the fitness landscape. A key idea is the deployment of the peak shift principle and ultra normal stimuli in perception that amplify otherwise marginal selection pressures for markers and trigger features (including facial expression, gestures and emotional vocalization).
We suggest early in primate evolution grunts, barks, screams, hoots, growls, howls screeches - formed an early emotional vocabulary (meaning inferred by ethologists based on social context). Intriguingly we have preliminary evidence that naive humans can, in a binary choice task, identify better than chance even subtle distinctions e.g. dominance vs aggression (gorillas), anger vs fear (chimps), separation vs aggression (vervets), even though they diverged from us 6 to 15 million years ago (vervets also appear to use onomatopoeia for birds vs. leopards). The emotional vocabulary then evolved via ‘peak shift’ and ultra normal (‘gull chick striped beak’;

exploiting idiosyncratic aspects of brains wiring for feature detection) principle, into an entirely novel "primordial language " of emotions - prosody and intonation which we find can convey a surprising range of emotional subtleties (e.g. REALLY. can be ironic, incredulous, skeptical, etc; there are 17 meanings. Another example NO. See website CBC). This preceded left-hemisphere language, but in parallel it evolved, via peak shift/ ultra normal modulation, into musical scales exemplified in Indian ragas, or, scales. Thus, the separation cry of a baby chimp morphed into Darbari Kanada (a scale) for existential angst of separation from God. (untutored westerners can distinguish ragas evoking closely related emotions - e.g. “personal present anguish” vs “our race has gone through great pain”; (mukhari and nagagandhari). Meanwhile the left hemisphere evolved Chomskys recursiveness, hierarchical embedding, but borrowed intonation from the right, so we don't sound like R2D2 or Siri.



Disclosures: V.S. Ramachandran: None. **S. Kandalaft:** None. **K. Vayyala:** None. **C. Chunharas:** None. **Z. Marcus:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.19/III45

Topic: H.02. Human Cognition and Behavior

Support: ERC Advanced grant no 669820

Title: Onset-driven activation of lexico-semantic cohorts dynamically activates bilateral fronto-temporal language systems

Authors: *A. CLARKE, L. K. TYLER, B. RANDALL, E. KOCAGONCU, W. MARSLEN-WILSON
Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Recognising spoken words requires the transformation of acoustic signals into a meaningful representation. Models of spoken word recognition propose that upon hearing the initial phoneme of a spoken word, there is rapid activation of the lexical and semantic properties of word candidates that match the initial sensory input. While recent research shows the STG analyses the phonetic features of speech inputs (Mesgarani et al., 2014), and MEG studies show how later stages of lexical and semantic cohort competition converge on the semantics of the target word (Kocagoncu et al., 2017), little is known about the neural dynamics of how auditory and phonetic inputs initially activate the lexical cohort. Here we use representational similarity analysis (RSA) of MEG data to reveal how the different aspects of spoken words are integrated into the recognition process from word onset. Participants heard 218 spoken nouns. We characterised the acoustic properties of each word from the sound recordings, and its phonological properties according to its phonetic features. To define the lexical candidates of the cohort, an independent set of participants performed a word gating study. Participants were presented with sound fragments of differing lengths and had to guess what the word was. The guesses represent the candidate set of likely words given the sound fragment, and the cohort size was the number of unique candidates. We defined the semantic properties of the cohort as the average of the Baroni and Lenci (2010) co-occurrence semantic feature vectors for each cohort member. RSA models were constructed for these acoustic, phonetic, lexical, and semantic dimensions. Spatiotemporal searchlight RSA was applied to source reconstructed MEG signals aligned to word onset. Early model-fit related to the loudness of the acoustic signal is seen in bilateral STG at 50 ms, along with model fit driven by the phonetic features of the word-initial phoneme. This onset-related phonetic model fit spread rapidly through STG and MTG, with bilateral frontal engagement within 150 ms. Cohort size showed effects starting at 80 ms but later than phonetic model fit in STG and moving into MTG within 200 ms, while cohort semantic effects appeared after 150 ms in STG/MTG. The prolonged and widespread model fit for the first

phoneme RSA suggests that speech onsets immediately trigger cascaded processing of lexical and semantic properties of word candidates in bilateral fronto-temporal language systems. Our results track the flow of information from pre-lexical properties of spoken words to abstract lexical and semantic representations, directly captured as spatio-temporally distributed activity patterns.

Disclosures: A. Clarke: None. **L.K. Tyler:** None. **B. Randall:** None. **E. Kocagoncu:** None. **W. Marslen-Wilson:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.20/III46

Topic: H.02. Human Cognition and Behavior

Support: Facebook Sponsored Academic Research Agreement

Title: End-to-end decoding of speech from human cortex

Authors: *J. G. MAKIN[1], E. F. CHANG[2]
[1]Ctr. for Integrative Neurosci., Univ. of California, San Francisco, San Francisco, CA;
[2]Neurosurg., UCSF, San Francisco, CA

Abstract: We aim to decode speech from cortical activity, an enterprise with both scientific and practical implications. In our case, data come from human electrocorticography (ECoG) recordings from from peri-Sylvian speech cortices. Taking a cue from recent advances in machine translation and automatic speech recognition, we implement and train a recurrent neural network (RNN) that maps from high-gamma activity directly to linguistic outputs, either words or full sentences. The RNN uses an encoder-decoder framework in order first to build abstract sentence representations from ECoG data, and then to decode these representations into text sentences. The network is trained to reduce the cross-entropy of the next word, given its current state and the previous word, and then evaluated on word-error rates for full sentences. We also show how to use *transfer learning* to overcome limitations on data availability; in particular, we show that decoding performance can be improved by training the network on multiple patients, despite very different electrode coverage. We likewise explore the usefulness of pre-training the network on different translation tasks.

Disclosures: J.G. Makin: 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.; funding was provided by a research contract under Facebook's Sponsored Academic Research Agreement.

E.F. Chang: 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.; funding was provided by a research contract under Facebook's Sponsored Academic Research Agreement.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.21/III47

Topic: H.02. Human Cognition and Behavior

Title: Spatiotemporal characteristics of semantic processing: An fMRI and EEG study of sentence comprehension

Authors: *K. S. ABOUD, L. E. CUTTING
Vanderbilt Univ., Nashville, TN

Abstract: In order to understand a sentence, a person needs to (1.) retrieve the meaning of a word from long-term memory ("semantic retrieval), and (2.) unite incoming word meanings into a coherent, internal representation of the text ("semantic integration"). While single modality neuroimaging studies have identified key brain areas that support these processes, there is still considerable debate over the specific roles these areas play during semantic cognition. Multimodal imaging techniques provide a powerful way to convergently identify the neural mechanisms of semantics. However, no studies to date have used multimodal imaging techniques to quantitatively compare the spatiotemporal signatures of retrieval versus integration networks. In the current study, we used functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to examine typical adult readers (n = 30) as they performed a novel sentence reading paradigm. In order to isolate areas specific to semantic retrieval and integration, sentences were manipulated to have variable word- and/or sentence-level semantic coherence. Findings revealed that semantic retrieval and integration independently map on to distinct neural routes in the bilateral fronto-temporal language system, and these circuits correspond with differential characteristics of the N400 temporal component. This is the first study to use fMRI/EEG to provide a unified spatiotemporal characterization of semantic sub-processes. Future studies will examine how these spatiotemporal signals correspond with individual differences in comprehension ability.

Disclosures: L.E. Cutting: None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.22/III48

Topic: H.02. Human Cognition and Behavior

Title: Pauses and neural indicators during speech: English (l1/l2), Spanish (l1/l2), and Heritage Spanish

Authors: *N. ENRIQUEZ[1], F. LLORELLA[2], J. CRUZ[1], L. DIAZ[3]
[1]Univ. of Houston, Houston, TX; [2]Univ. of Gerona, Gerona, Spain; [3]Univ. Pompeu Fabra, Barcelona, Spain

Abstract: In this paper we present a study on processing problem indicators in oral production in both Spanish and English in a simulated transaction task. Subjects are native English, native Spanish and heritage Spanish speakers. The aim was to describe the role of speech pauses as processing indicators in oral production as a communication strategy and their differences between groups of speakers and the language used in the simulation.
Hypotheses: i) pauses are different quantitative and qualitatively depending on the speaker's competence; ii) familiarity with the situation in the target language affects the patterns of occurrences of pauses; iii) the speaker's role in the task (operator or costumer) affects the number and function of pauses and iv) pragmatic and cultural aspects do play a role in the amount and type of pauses in each language.
In order to test these hypotheses, we gathered two different corpora. StopELE/SP (6031 tokens) which consists of a sample of 18 dialogues in Spanish (6 native, 6 heritage and 6 non-native) and StopELE/EN (5562 tokens) which contains 18 dialogues in English (6 native, 6 heritage and 6 non-native). The speakers played both roles in both languages.
We report preliminary findings on EEG data (64 channels, 500 Hz) during oral production. The bandpower in EEG data during 36 speech pauses was compared to baseline, where the subjects relaxed and looked at a blank paper in front of them for 1 min. The data was preprocessed by using the H-inf filter to remove eye-related artifacts, band-pass filtering the signal between 0.3 and 50 Hz, using the PREP pipeline for robust re-referencing, and ASR for removal of artefactual power bursts. At the onset of the speech pauses we found statistically significant ($p<0.01$) modulation in the left frontal areas for the delta band (1-4Hz), and activation of central-left regions in the alpha (8-12 Hz) and gamma (30-50 Hz) bands. The pattern was found both in English and Spanish speech production, with pre-frontal bandpower deactivation in the English task.
Linguistic data confirms the role of pauses as indicators of the difficulty of the task itself and the linguistic difficulty in carrying it out in L2, and by role, as stated in hypothesis (i), (ii) and (iii) above. The study also reveals significant differences between native, heritage and non-native

speakers, related to hypotheses (i) and (iv). Specifically, in native speakers, pauses are indicators of difficulty in management decisions, while in non-native speakers pauses indicate difficulties with syntax, verb inflection and information management.

Disclosures: F. Llorella: None. **J. Cruz:** None. **L. Diaz:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.23/III49

Topic: H.02. Human Cognition and Behavior

Support: Undergraduate Ronald E. McNair Post Baccalaureate Achievement Program
Robert Wood Johnson Foundation
W.H. Coulter Eminent Scholar Fund
Adaptive Neural System Laboratory

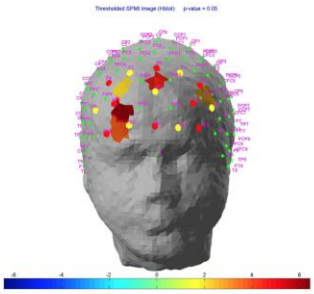
Title: Language proficiency and executive function: An fNIRS study

Authors: *V. DARGAM[1], M. BARALT[1], A. DARCY MAHONEY[3], R. JUNG[2], A. K. THOTA[2], L. RINCON GONZALEZ[1], C. MYLAND[1], V. LEON[1]
[2]Biomed. Engin., [1]Florida Intl. Univ., Miami, FL; [3]The George Washington Univ. Sch. of Nursing, Washington, DC

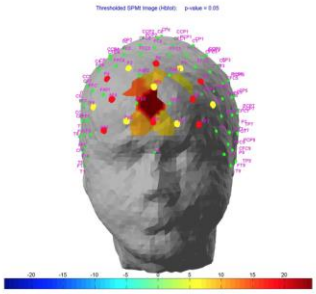
Abstract: Robust empirical evidence continues to show a bilingual 'edge'; in executive functioning. However, to date, no research has explored the potential for a bilingual edge in executive functioning with heritage speakers, who may have learned Spanish first as children, but who are now dominant in English and who have receptive knowledge only in Spanish (e.g. Montrul, 2004). The present study aims to contribute to this gap in the literature by comparing the executive functioning of 1) monolingual, 2) fully productive bilingual, and 3) heritage speakers (understand Spanish but do not productively speak it) of English and Spanish. 45 adults ages 18-25 participated in the study (25 were females). Participants performed two tasks that measured executive function: the Dimensional Card Change Sort Task (DCCS) and the Go/No-Go task, with simultaneous brain imagining via Functional Near-Infrared Spectroscopy (fNIRS). Preliminary fNIRS data revealed that bilinguals demonstrated greater neural recruitment efficiency than the monolinguals and the heritage speakers. Monolinguals and bilinguals shared some areas of neural recruitment while performing the tasks, whereas heritage speakers did not. For both the DCCS and Go/No-Go tasks, heritage speakers had the slowest reaction times when compared to the other groups; the bilinguals were the fastest. These data indicate two key results. First, bilingualism results in enhanced executive functioning in the brain. Second, this bilingual benefit requires full *productive* capacity in two languages, not just receptive knowledge, as is the

case for the heritage learner profile. The implications of our study suggest that bilingualism can lead to enhanced executive functioning, but that daily oral use is required to reap the benefits of bilingualism. We conclude with implications for bilingual education in the U.S., and in particular, with a discussion on the unique linguistic profile and needs of heritage speakers.

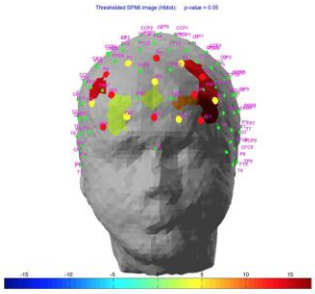
A General Linear Model was used to find contrast SPM image to find similar areas of neural activation per language groups. Hbtotal statistically significant t-statistic values compared No-Go to Go task per participant. Monolinguals and bilinguals had common areas of neural activation while heritage speakers did not.



Example of a **Monolingual's** SPMt image.



Bilingual



Heritage Speaker

Disclosures: V. Dargam: None. **M. Baralt:** None. **A. Darcy Mahoney:** None. **R. Jung:** None. **A.K. Thota:** None. **L. Rincon Gonzalez:** None. **C. Myland:** None. **V. Leon:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.24/III50

Topic: H.02. Human Cognition and Behavior

Support: MOST 106-2420-H-010 -002 -MY2

Title: Proficiency in a second language modulates the engagement of the first language network

Authors: *Y.-C. LIN[1], F.-H. LIN[2], W.-J. KUO[1]
[1]Inst. of Neurosci., Natl. Yang-Ming Univ., Taipei, Taiwan; [2]Inst. of Biomed. Engin., Natl. Taiwan Univ., Taipei, Taiwan

Abstract: During the second language (L2) learning, neural circuits need to be rewired to process new statistical structure and grammatical properties. Therefore, the learning performance, i.e. L2 proficiency, must couple with the functional changes of the brain network for L2 processing. This study investigates changes in brain networks for L2 spoken sentences

processing. Two groups of native Mandarin speakers participated in an functional magnetic resonance imaging (fMRI) experiment. The two groups differed in L2 proficiency (High- and Moderate-proficiency, henceforth: H-group and M-group, respectively) meanwhile had similar educational history and learned English as their L2 after the age of seven (late learners). Their language skills and learning history were evaluated via an online questionnaire. In the fMRI experiment, participants passively listened to sentences in the native language (L1), L2, and Wolof (served as an unknown control language to the participants). The online questionnaire showed that the H-group had better L2 skill than the M-group, implying that the H-group understand L2 materials better. Our fMRI results showed that when listening to spoken sentences in L2, the H-group recruits the language network resembling the network elicited by L1. On the contrary, the M-group shows compelling different activity patterns when listening to spoken sentences in L1 and L2. Significant activations in the bilateral temporal regions were only found in the L1 but not L2 condition. Surprisingly, we found that, from moderate to proficient of L2, the cortical areas covary with L2 proficiency levels migrate from language areas related to higher levels to lower levels processing. In the M-group, we found L2 proficiency positively correlated with the cortical response in the middle temporal gyrus and bilateral angular gyri, which were found to be related to semantic and syntactic processing. In the H-group, the positive correlation was revealed in the left early auditory cortex and the left superior temporal gyrus which was identified to play a central role of identifying spoken word forms. Our results suggest that the brains in different status of L2 proficiency might underwent various stages of functional improvement to grow the efficiency of spoken sentence comprehension. In summary, by contrasting participants with different L2 proficiency, we successfully identified distinct brain regions recruited for supporting the comprehension of spoken sentences in different stages of L2 learning.

Disclosures: Y. Lin: None. **F. Lin:** None. **W. Kuo:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.25/III51

Topic: H.02. Human Cognition and Behavior

Support: Toyota Motor Corporation Grant

Title: Assessment of neural networks related to post-stroke aphasia with the EEG phase synchrony index

Authors: *T. KAWANO[1,2,3], N. HATTORI[2,4,1,3], Y. UNO[3], M. HATAKENAKA[1], H. YAGURA[1], H. FUJIMOTO[1], T. YOSHIOKA[1], M. NAGASAKO[1], H. OTOMUNE[1], H. MOCHIZUKI[2], K. KITAJO[3], I. MIYAI[1]

[1]Neurorehabilitation Res. Inst., Morinomiya Hosp., Osaka-Shi, Japan; [2]Dept. of Neurol., Osaka Univ. Grad. Sch. of Med., Osaka, Japan; [3]Rhythm-based Brain Information Processing Unit, CBS-TOYOTA Collaboration Ctr., RIKEN Ctr. for Brain Sci., Saitama, Japan; [4]Endowed Res. Dept. of Clin. Neuroengineering, Global Ctr. for Med. Engin. and, Osaka Univ., Osaka, Japan

Abstract: Objective: Neural network function can be assessed by the EEG-based synchrony analysis. We have reported that the EEG phase synchrony index (PSI) between specific electrodes showed correlations with various impairments in post-stroke patients. The aim of the current study was to assess networks related to aphasia by using the PSI.
Methods: Twenty-four first ischemic stroke patients presenting aphasia with left hemispheric lesions (all right handed, mean age: 67.4, median post-stroke days: 37.5) and age-matched 22 healthy volunteers were enrolled. Patients were assessed using two subscore sets (speech score: 0–70; comprehension score: 0–50) of the Standard Language Test of Aphasia. We obtained 2.5 minutes of eye-closed EEG data with electrodes placed according to the international 10–20 system, and computed the PSIs in six frequency bands (δ, θ, α, β1, β2, and γ). Then we calculated the PSIs of following four electrode pairs associated with language networks: 1 bilateral inferior frontal lobes (F7F8), 2 bilateral superior temporal lobes (T5T6), 3 ipsilesional front-temporal lobes (F7T5), and 4 contralesional front-temporal lobes (F8T6). We evaluated abovementioned networks by correlations between the PSIs and clinical scores. Spearman's rank correlation coefficient with Bonferroni correction was used for the correlation analysis.
Results: 1: The interhemispheric PSIs were positively correlated with clinical scores, whereas the intrahemispheric PSIs were negatively correlated with clinical scores. 2: In all electrode pairs, the PSIs were correlated with speech score (F7F8: P=0.034; T5T6: P=0.035; F7T5: P=0.0035; F8T6: P=0.035). 3: In electrode pairs not including left inferior lobe (T5T6/F8T6), the PSIs were correlated with comprehension score (T5T6: P=0.038; F8T6: P=0.005). 4: Correlations were observed in distinct frequency bands (F7F8: β1, T5T6: β1, F7T5: β2, F8T6: σ). 5: Additionally, F8T6-PSI was significantly larger than that of normal control (P=0.004, Mann-Whitney U-test).
Conclusion: Existence of both positive (interhemispheric PSIs) and negative (intrahemispheric PSIs) correlations suggested different roles of these networks. In addition, the PSIs including left inferior frontal lobe were correlated with speech score, but not with comprehension score, in accordance with the role of this area (speech production). Furthermore, elevated F8T6-PSI compared with normal control suggested active role of the contralesional hemisphere in the post-acute aphasia. Taken together, we concluded that the EEG PSI helps us understand the mechanisms of post-stroke aphasia from a network point of view.

Disclosures: T. Kawano: None. **N. Hattori:** None. **Y. Uno:** None. **M. Hatakenaka:** None. **H. Yagura:** None. **H. Fujimoto:** None. **T. Yoshioka:** None. **M. Nagasako:** None. **H. Otomune:** None. **H. Mochizuki:** None. **K. Kitajo:** 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.; Toyota Motor Corporation Grant. **I. Miyai:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.26/III52

Topic: H.02. Human Cognition and Behavior

Title: Effects of categorical cues on naming

Authors: *R. TANAKA[1], Y. ITAGUCHI[3], C. YAMADA[4], K. FUKUZAWA[2]
[1]Waseda Univ., Tokyo, Japan; [2]Waseda Univ., Shinjuku-ku, Japan; [3]Dept. of Syst. Design and Engin., Keio Univ., Kanagawa, Japan; [4]Waseda Univesity, Tokyo, Japan

Abstract: Effects of categorical cues on naming Ryoko Tanaka, Yoshihiro Itaguchi, Chiharu Yamada, Kazuyoshi Fukuzawa Keywords: naming, picture naming, name agreement, category, language production The present study investigated effects of categorical cues on the performance in a picture naming task. Impairment in naming is one of the most common symptoms in aphasic patients. Although previous studies reported that categorical cues facilitate the performance in picture naming tasks, the effects of categorical cues in a naming task for Japanese healthy adults have never been investigated. We thus conducted an experiment to test the hypothesis that categorical cues improve naming performance also in Japanese healthy participants. Twenty university students participated in a picture naming task. In the experiment, participants were asked to name line drawings presented on a display as quickly as possible. We used 10 drawings for each of eight categories: vegetables and fruits, instruments, processed food (e.g. doughnuts, sandwiches), animals, commodity, vehicles, colors, and body parts. Participants were assigned to one of two groups: in one group they were given categorical cues and the cues were not given to the control group. For the group given a categorical cue, a name of a category was visually provided before drawings of the category were shown. One experimenter counted the number of correct responses and the reaction time was registered by a computer. We performed independent t-tests to compare the number of correct responses and the reaction time between the groups. The number of correct responses did not differ between the groups, maybe due to a ceiling effect. However, the reaction time was significantly shorter in the group with categorical cues. The results for the first time confirmed that categorical cues facilitated efficiency of naming in Japanese population.

Disclosures: R. Tanaka: None. **Y. Itaguchi:** None. **C. Yamada:** None. **K. Fukuzawa:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.27/III53

Topic: H.02. Human Cognition and Behavior

Support: University of Missouri Research Board Grant
University of Missouri Mission Enhancement Fund

Title: Stress alters functional connectivity in language processing regions of the brain during verbal fluency tasks

Authors: *N. NAIR[1], J. P. HEGARTY, II[3], B. J. FERGUSON[4], S. J. HOOSHMAND[2], P. HECHT[5], M. R. TILLEY[6], S. E. CHRIST[7], D. Q. BEVERSDORF[8]
[1]Dept. of Radiology, [2]Univ. of Missouri, Columbia, MO; [3]Dept. of Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA; [4]Thompson Ctr. For Autism, Columbia, MO; [5]Avanir Pharmaceuticals Inc., Aliso Viejo, CA; [6]Central Methodist Univ., Columbia, MO; [8]Dept Radiol, Neurol, Psychol Sci, DGS of INP, [7]Univ. of Missouri Columbia, Columbia, MO

Abstract: Psychological stress has deleterious effects on cognitive performance, especially in tasks that require searching through multiple, distributed networks. For example, verbal fluency tasks require rapid access to distributed lexical and semantic networks and our lab has previously shown that stress impairs performance in these tasks. This has implications for conditions such as public speaking and test taking anxiety. However, the neural correlates of the effects of stress during such language processing tasks are not well explored. This study explored stress effects on functional connectivity (FC) in specific language processing regions of the brain while performing verbal fluency tasks. Since serotonin transporter gene (5-HTTLPR) polymorphisms (S-allele and L-allele) and gender are known to influence stress susceptibility in individuals, we additionally explored the role of these two factors on the effect of stress on FC during task. Forty-five healthy volunteers attended two functional magnetic resonance imaging (fMRI) sessions. During the sessions, they performed two runs each of letter and category fluency tasks, interposed with either the Montreal Imaging Stress Test to induce stress or a no-stress control task. fMRI data was analyzed using FSL (FMRIB Software Libraries) software. The a priori regions of interest (ROIs) were the left and right inferior frontal gyri, left middle temporal gyrus, left parietal lobe and left fusiform gyrus. Significant regional variations in FC strength were noted between the a priori ROIs while performing verbal fluency tasks under stress. Overall, males displayed regional increases in functional connectivity strength over long and short distances during task under stress while S-allele participants, irrespective of gender, showed regional decrements in FC strength. This study is the first to explore the neural correlates of stress effects on language processing. Previous work from our lab has shown the potential for

specific therapeutic agents to overcome the cognitive deficits associated with stress. Larger studies examining neural correlates of stress susceptibility, its effect on task performance combined with therapeutic agents to reverse these effects could help pave the way towards targeted therapeutic interventions.

Disclosures: N. Nair: None. **J.P. Hegarty:** None. **B.J. Ferguson:** None. **S.J. Hooshmand:** None. **P. Hecht:** A. Employment/Salary (full or part-time):; Avanir Pharmaceuticals Inc., Aliso Viejo, California, USA. **M.R. Tilley:** None. **S.E. Christ:** None. **D.Q. Beversdorf:** None.

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.28/III54

Topic: H.02. Human Cognition and Behavior

Title: Wernicke aphasia patients do not understand that they do not understand language: An initial case study

Authors: *E. L. ALTSCHULER
Physical Med. and Rehabil., Metropolitan Hosp., New York, NY

Abstract: In 1874 Carl Wernicke described a novel form of aphasia whereby patients spoke fluently but (1) the speech was often simply gibberish, and (2) the patients did not often understand what was said to them. Wernicke described a third feature of the syndrome which remains of great interest and still not understood today: the patients do not seem bothered by the fact that they do not understand what others say, and that what they say cannot be understood. An outstanding question is whether or not Wernicke aphasia patients (WAP) appreciate, or not, their lack of understanding of language (or the intelligibility of their own speech). Recently we have described a method to answer this question (Hartman et al., and ELA, J Undergrad Neurosci Educ. 2017;16(1):E5-E12). In brief: As a control WAP are shown pictures of someone "speaking in pictures," that is, a cartoon of a person with a speech bubble containing a picture. For example, the picture might be of a bone. Then there are given three choices (also in pictures): a cat, a dog and a collection of question marks. The target answer is the dog. As reasoning appears to be intact in WA patients they should answer these questions on target all or most of the time. A subsidiary set of questions is next needed to establish that the WAP will choose the answer '????' on target, for example when asked to pick a picture of the weather outside given a picture a room with a shade covering the window. Finally, the patients are asked the original questions but now posed in words not pictures, e.g., 'bone'/'dog,' 'cat,' '????' . If the WAP knows she does not understand language, she will chose '????', but if the WAP does not know she does not understand language, she will randomly pick an answer. We have used this method in an initial case study of a patient with moderate WA (and expressive aphasia)

following stroke. For no question would the patient chose '????', so we had to modify our approach somewhat. When asked simple arithmetic questions written out in numerals the patient chose the correct answer at a level three standard deviations above chance. However, when asked the same questions written out in words (answers in words as well), the patient performed at chance. Finally, we interspersed questions with no correct answer. When the questions (and answers) were given as numerals, the patient got visibly perturbed and started gesticulating at the examiner, but when questions were posed as words the patient did not exhibit this behavior. In this case it thus appears that a WA patient does not appreciate their lack of language understanding. Further studies are warranted.

Disclosures:

Poster

695. Human Cognition and Behavior: Language

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 695.29/DP13/III55

Topic: H.02. Human Cognition and Behavior

Title: Behavioral and electrophysiological evidence of incidental learning, generalization and retention of speech categories from continuous speech

Authors: *C. WU[1], R. LIU[3], S.-J. LIM[4], L. L. HOLT[2]
[1]Psychology, [2]Carnegie Mellon Univ., Pittsburgh, PA; [3]MARi, Washington, D.C., DC; [4]Speech, Language and Hearing Sci., Boston Univ., Boston, MA

Abstract: Speech segmentation and speech category learning are each been described in rich literature. Yet, few studies have examined how these two challenges affect learning in the same context. In the current study, native English participants played a video game shown in prior work to encourage incidental learning of speech categories, even in the context of fluent speech requiring segmentation. Here, 4 acoustically-variable Mandarin keywords were embedded in 4 distinct sentences uttered by 4 talkers (2 female). Unknown to participants, the presence of a keyword in the continuous Mandarin speech was associated with functionally- relevant actions and events in the game. During training, participants were not informed about the keywords, made no overt categorization decisions, and received no feedback. An overt post-training categorization test demonstrated robust incidental keywords learning that persisted even 10 days after training, and generalized to novel utterances and talkers. Further, the N100 response in the frontal and central EEG electrode (Fz and Cz) evoked by keyword onsets within continuous Mandarin speech during passive listening was greater post-training compared to pre-training. This enhancement was not observed for Mandarin words that were frequency-matched but not functionally paired with a visual referent in video game training.

Disclosures: C. Wu: None. **R. Liu:** None. **S. Lim:** None. **L.L. Holt:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.01/III56

Topic: H.02. Human Cognition and Behavior

Support: PredictAble (Marie Curie Innovative Training Networks no. 641858)
ChildBrain (Marie Curie Innovative Training Networks no. 641652)
MultiLeTe (Academy of Finland #292 466)

Title: Developmental changes in speech perception at the syllable, word and sentence level

Authors: *O. B. KOLOZSVÁRI[1,2], W. XU[1,2], N. LOULELI[1,2], N. AZAIEZ ZAMMIT CHATTI[1], J. A. HÄMÄLÄINEN[1,2]
[1]Dept. of Psychology, Univ. of Jyväskylä, Jyväskylä, Finland; [2]Ctr. for Interdisciplinary Brain Res., Jyväskylä, Finland

Abstract: During auditory speech perception, the brain extracts speech sounds and their sequences from the incoming auditory signal, which then activate the meaning of the word. Using EEG and MEG, acoustic-phonetic features of speech have been found to modulate activity in the auditory cortices as seen in the N100m response around 50-100 ms. Language-specific phonetic-phonological analysis has been shown to start 100-200 ms following stimulus onset. From 200 ms onwards studies have found sensitivity to lexical-semantic manipulations in the superior temporal areas.
In our study, we wanted to investigate the developmental changes of evoked fields reflecting speech perception in children (between ages of 5 and 8). As the first step of analysis, we investigated differences in sensor-level responses, with a focus on event-related-fields to syllables and words. In the future we will also examine source level responses and neural entrainment at the word and sentence level.
Here, we report data from 11 five-year-old (4 boys) and 23 eight-year-old (11 boys) Finnish children. Participants were measured with a whole-head 306 channel Elekta Neuromag TRIUX MEG device. Planar gradiometer data were transformed into combined planar gradients and used in the analyses. Pre-processing was done using MNE for Python and analyses were done using FieldTrip toolbox for MatLab.
During the measurement, participants were asked to listen to syllables (18 repetitions of /ka/, /pa/ and /ta/), words (starting with the syllables, 18 different words for each syllable) and sentences (1 sentence for each word) presented through earphones while looking at a fixation cross. Their task was to repeat out loud what they had just heard when a cue (a parakeet) was presented on the screen. 54 stimuli per type of stimuli were presented in random order.

Permutation tests with channel and time point clustering were carried out. (Time window of analysis: 0 - 500 ms, cluster α level .05, number of permutations 3000.)
Our permutation tests showed significant differences between age groups to Syllable stimuli in the P1-N1 (p=0.011), N2 (p=0.021) and N4 (p=0.021) time-windows in the fronto-central channels and to Word stimuli in the P1-N1-N2 (p = 0.006) and N4 (p = 0.007) time-windows in the front-central channels.
Our findings show significant differences between the two groups, in case of both types of stimuli. The N1m response was larger for 8-year-olds than for 5-year-olds when presented with syllables or words. These differences seem to be robust and they appear to reflect developmental changes in speech perception between the two age groups.

Disclosures: O.B. Kolozsvári: None. **W. Xu:** None. **N. Louleli:** None. **N. Azaiez Zammit Chatti:** None. **J.A. Hämäläinen:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.02/III57

Topic: H.02. Human Cognition and Behavior

Support: NIDCD Grant R01DC012797

Title: Effects of early sign language use on anatomical structures of visual regions: Surface-based and DTI analyses

Authors: *Q. CHENG[1], D. KLEIN[2], J.-K. CHEN[2], E. HALGREN[1], R. I. MAYBERRY[1]
[1]UCSD, La Jolla, CA; [2]McGill Univ., Montreal, QC, Canada

Abstract: Sign language is a visuospatial language that requires motion processing, and often involves more peripheral visual processing for proficient signers. Previous studies find that deaf people with early sign language often show better peripheral vision, and also show more activation of the left middle temporal and medial superior temporal (MT/MST) regions when processing motion (Bavelier et al. 2001, 2006; Bosworth & Dobkins 1999). It is unclear whether these enhancements come from compensatory plasticity for auditory deprivation, or from extensive early sign language use. Early sensory and language deprivation during a critical period often have a significant impact on brain development (Hensch 2005; Mayberry et al 2011, 2018). By investigating the brain structures of deaf individuals with various ages of sign language onset, the present study explicitly examines the effects of age of sign language acquisition (AoA) on brain plasticity in visual regions. A group of 22 deaf signers with varying AoAs but similar years of sign language use participated in the study. Structural T1 and diffusion-weighted data were collected and corrected using in house pipelines and FSL (Smith et

al. 2006). For T1 data, we used a topographical visual map (Wang et al. 2015) to parcellate the visual regions in Freesurfer (Fischl et al. 2002). For DTI data, we used the group connectometry analyses in DSI Studio (Yeh et al. 2015). Using gender and age as covariates, the surface-based analyses showed a significant negative AoA effects on volume at one lateral-temporal region, MST ($t = -4.71$, $p < 0.001$), where neuronal firing encodes coherent motion, and significant negative effects ($p < 0.01$) at several ventral-lateral regions (V2v, V3v, PHC1). For the DTI analyses, also with gender and age as covariates, we found AoA to be significantly related to decreased fiber connectivity in the left inferior longitudinal fasciculus, especially in the lateral portion near the middle temporal lobe. These findings suggest that early sign language experience is crucial for neural plasticity in regions for para/peripheral vision and motion processing in deaf brains. Missing the critical time window for sensory-linguistic input has an irreversible impact on brain structures that support sign language learning and processing, which may partially explain the disrupted language outcomes of these deaf individuals (Boudreault & Mayberry 2006).

Disclosures: D. Klein: None. **J. Chen:** None. **E. Halgren:** None. **R.I. Mayberry:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.03/III58

Topic: H.02. Human Cognition and Behavior

Support: Marie Curie Innovative Training Networks, No. 641858
eSeek project (Internet and learning difficulties: A multidisciplinary approach for understanding reading in the new media)

Title: Brain responses to native and non-native syllables in typical readers and in children with reading or attentional problems

Authors: *N. AZAIEZ ZAMMIT CHATTI, O. H. LOBERG, N. LOULELI, O. B. KOLOZSVÁRI, J. A. HÄMÄLÄINEN, P. H. LEPPANEN
Univ. of Jyväskylä, Jyväskylä, Finland

Abstract: Previous research has demonstrated that speech perception is linked to basic reading skills. In this study, we explored this link in school children with dysfluent reading or attentional problems using a cross-linguistic approach. Brain event-related potentials (ERPs) of 138 sixth grade Finnish children were recorded with a high-density Electroencephalography (EEG) system (128 electrodes) in three groups: 86 typical readers, 26 dysfluent readers and 17 children with attentional problems. Participants were exposed to native (Finnish) and non-native (English) language stimuli in an auditory oddball paradigm presented in two different blocks. In the first

block, Finnish syllables were used as stimuli, /suu/ as standard (80%), /sai/ and /sii/ as deviant stimuli (10% each). In the second block, non-native phonologically matched syllables were used instead, /shoe/ (80%), /shy/, and /she/ (10% each). Cluster-based permutation statistics for ERP waveforms and topographic maps were calculated between the different conditions and between the different groups. Our results showed that ERP responses were different between languages (Finnish vs English) and within language: in Finnish (/sai/ vs /sii/) and in English (/shy/ vs /she/) for the three groups. The brain responses to the non-native syllables were different compared to the responses observed with the native stimuli. Moreover, ERP amplitudes, latencies and topographical distribution were different between the three groups. The participants with attentional problems and dysfluent readers showed atypical brain activities compared to the typical readers. Overall, these atypical responses suggest less specific phonemic representations and more reliance into stimulus features during passive auditory processing. Next steps involve further investigation of these neural signatures by localizing their sources and examining their correlation to behavioral measures.

Disclosures: N. Azaiez Zammit Chatti: None. **O.H. Loberg:** None. **N. Louleli:** None. **O.B. Kolozsvári:** None. **J.A. Hämäläinen:** None. **P.H. Leppanen:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.04/III59

Topic: H.02. Human Cognition and Behavior

Support: Marie Skłodowska-Curie Actions (MSCA) Innovative Training Network (ITN), no. 641858

Title: Morphological representations in pre-school children with and without risk for dyslexia

Authors: *N. LOULELI[1], L. NIEMINEN[2], N. AZAIEZ ZAMMIT CHATTI[1], O. B. KOLOZSVARI[1], J. A. HÄMÄLÄINEN[1], P. H. T. LEPPÄNEN[1]
[1]Dept. of Psychology, Univ. of Jyvaskyla, Jyvaskyla, Finland; [2]Ctr. of Applied Language Studies, Univ. of Jyvaskyla, Jyvaskyla, Finland

Abstract: Phonological processing and speech perception difficulties have been associated with dyslexia, but there is considerable diversity across dyslexics in their cognitive skill profiles (e.g. dyslexics with and without phonological difficulties). While the morphological representations are closely linked to phonological representations and speech perception, it is possible that a subgroup of dyslexics have problems primarily with morphological processing. This study aims to investigate the connection between phonology, morphology and dyslexia in Finnish language by testing pre-school children using magnetoencephalography (MEG). Event-related fields

(ERFs) were measured from 37 pre-school 6.5-7 year-old Finnish children consisting of two groups: 20 typically developing control children without risk and 17 with familial risk for dyslexia. Children were auditorily presented with a morphological task during MEG recording: 108 pairs of sentences, consisting of a verb and its stem with the derivational suffix -jA, which transforms a verb into a noun (Hän johtaa. Hän on johtaja - He leads. He is a leader.). The derivational nouns were also divided into two subcategories, legal and illegal forms. Illegal word forms were the same as legal word forms (johtaja), but with a morpho-phonological change in the last vowel before the derivational suffix (johtija). The morphologically legal and illegal forms produced distinct ERFs for both groups, but the timing of the brain responses and the topography of the brain activation differed between the groups. Right hemispheric activation was more dominant in the control group, whereas bilateral hemispheric activation was observed in the group at-risk for dyslexia. Furthermore, the effect of the morphological manipulation was 250 ms delayed in children at risk for dyslexia compared to the control children. These findings suggest differences in decoding of the morphological information, already before school entry, in children at risk for dyslexia.

Disclosures: N. Louleli: None. **L. Nieminen:** None. **N. Azaiez Zammit Chatti:** None. **O.B. Kolozsvari:** None. **J.A. Hämäläinen:** None. **P.H.T. Leppänen:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.05/III60

Topic: H.02. Human Cognition and Behavior

Support: PAPIIT-IN304417

Title: Children with Down syndrome anticipate information

Authors: *N. ARIAS-TREJO[1], A. A. ANGULO-CHAVIRA[2], J. B. BARRÓN-MARTÍNEZ[1]
[1]Facultad de Psicología, Lab. de Psicolingüística, UNAM, Mexico City, Mexico; [2]Inst. de Neurociencias, Univ. de Guadalajara, Guadalajara, Mexico

Abstract: Under typical development, children and adults employ linguistic information to anticipate information. Whether children and young people with an intellectual disability that impairs language anticipate information based on verbal cues remains unspecified. This research investigates if children and young adults with Down syndrome are able to anticipate information based on the semantic information of verbs. People with this genetic syndrome tend to exhibit problems at producing language; however, their comprehension remains optimal according to their mental age. However, although their comprehension is explored for all grammatical categories when using parental reports, it is generally restricted to the quantification of nouns

when observational or experimental studies are employed. Thus, we employed a preferential-looking study presented by means of an eye-tracker to explore whether beyond problems to produce words, particularly verbs, children and teenagers employ the meaning of verbs to anticipate a target, in the same fashion as typically-developed children do. Therefore, we compared their performance to a control group matched by mental age. In ten trials, the participants saw two images -target and distractor-, while they heard a phrase containing a semantically informative verb (e.g., 'eat') or an uninformative verb (e.g., 'see'). The results showed that the two groups of children, matched for a mean mental age of 5.48 years, were able to anticipate the target upon hearing an informative verb, moreover prediction skills were positively correlated with mental age in those with Down syndrome. As expected, when exposed to uninformative verbs, participants were unable to systematically anticipate a target. This work demonstrates that children and teenagers with Down syndrome are capable of predicting information based on the semantic information of verbal cues. We also show that sentence processing in this population, as in typical development, is driven by predictive relationships between verbs and arguments.

Disclosures: N. Arias-Trejo: None. **A.A. Angulo-Chavira:** None. **J.B. Barrón-Martínez:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.06/III61

Topic: H.02. Human Cognition and Behavior

Support: Supplement to NIH Grant R01 HD081078

Title: An fMRI study of the cerebellum during reading in children and adults

Authors: *S. ASHBURN[1], L. D. FLOWERS[1], E. M. NAPOLIELLO[1], G. F. EDEN[2]
[2]Ctr. for the Study Learning, [1]Georgetown Univ., Washington, DC

Abstract: It is well established that left inferior frontal, temporo-parietal, and occipito-temporal cortices play a role in reading (Pugh et al., 2001). A meta-analysis of brain imaging studies of reading in adults found convergence of activity in these areas, but also in bilateral cerebellum (Martin et al., 2015). However, the cerebellum was not observed in children, raising the question whether it is specifically involved in experienced adult readers. Here we approached this question by examining *activation* as well as *functional connectivity* (FC) in *typically reading adults* (n=35, age 23.02 ± 3.2). We contrasted an implicit word reading task with a pseudofont control task (Price et al., 1996) and expected the cerebellum (1) to be *active during reading*, and (2) have *functional connections* with those cortical regions known to be involved in reading. We

also compared a subset of these adults (n=20, age 24.61 ± 2.7) with children (n=20, age 9.80 ± 1.9) matched on IQ, and expected *greater activity and FC in adults compared to children*.
First, the *activation* analyses examined (a) whole cerebellum as well as (b) six cerebellum sub-regions (left and right crus I, crus II, and lobule VI; p-FWE < .05, height threshold < .001) using SUIT, within SPM12. Both analyses revealed no cerebellar activation in the full sample of adults. As such it was not surprising that when comparing the subset of adults with the children, there were no between-group difference in either direction (even though, unexpectedly, in children the within-group subregion analysis revealed left lobule VI activation). Since the meta-analysis (Martin et al., 2015) had used low-level baselines, we also compared our reading task with a fixation baseline and again found no between-group differences for either whole or subregion cerebellar analyses.
Second, we performed ROI-to-ROI *generalized psychophysiological interaction FC* analyses with the CONN toolbox in both groups, with the 6 subregions as seeds, and 7 cortical regions known to be active during reading as target ROIs (seed-level corrected p-FDR <.05). In the full sample of adults we found only de-correlation between left crus I and left superior parietal lobule. We found no between-group differences when comparing the subsample of adults with the children (and there was no FC in the group of children).
Overall, our results suggest that in adults the cerebellum is not involved in single word processing and there is no positive FC between the cerebellum and cortical regions known to be involved in reading during word reading. We also found no differences between adults and children, together suggesting that an adult-specific role of the cerebellum for reading is not likely.

Disclosures: S. Ashburn: None. **L.D. Flowers:** None. **E.M. Napoliello:** None. **G.F. Eden:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.07/III62

Topic: H.02. Human Cognition and Behavior

Support: Medical Research Council programme grant numbers G03000117/65439
CHRAT studentship

Title: Functional MRI of language lateralisation in developmental amnesia

Authors: *S. M. BUCK[1], T. BALDEWEG[2], R. ELWARD[5], D. CARMICHAEL[3], F. VARGHA-KHADEM[4]
[1]Inst. of Child Hlth., London, United Kingdom; [2]Cognitive Neurosci. and Neuropsychiatry,

[3]Developmental Imaging and Biophysics, [4]UCL Inst. of Child Hlth., London, United Kingdom; [5]Cognitive Neurosci. and Neuropsychiatry, UCL Instite of Child Hlth., London, United Kingdom

Abstract: Introduction Evidence suggests that despite their close interaction, the hippocampal network serving cognitive memory, and the neostriatal-prefrontal network serving speech and language are distinct in their functions. A theoretical question is whether early damage to the hippocampus alters not only the fMRI activation of cognitive memory, but also, indirectly, that of the speech and language network. Functional MRI study of patient Jon, who has developmental amnesia (DA) caused by bilateral hippocampal atrophy consequent to neonatal hypoxia-ischaemia, showed that similar to controls, he successfully retrieved autobiographical memories using both medial and lateral brain regions. However, unlike controls who showed left-sided activation, Jon showed bilateral activation of this network which includes several regions involved in speech and language functions (Maguire et al., Brain, 2001). Here, we used fMRI to ascertain the status of language lateralisation for encoding and retrieval of auditory verbal stimuli in patients with DA compared to controls. **Methods** Functional MRI correlates of language lateralisation were acquired on a 3T Siemens system in five patients with DA (n = 5, age range 8-40 years), and healthy controls (n = 27, age range 8 to 18 years). Language lateralisation was assessed through verb generation, where nouns were heard one at a time (one every 4 sec) and participants required to overtly generate a verb for each noun (*e.g.* hear "cake", generate "eat"). **Results** In the controls, block-wise comparisons for the language task demonstrated activations in left Broca's, and Wernicke's areas ($p<0.05$, FWE; Laterality Index Broca's area = 0.79). Consistent with this finding, patients with DA showed activation in left Broca's area, albeit with some weaker activation in the homologous region in the right hemisphere ($p<0.05$). Bilateral representation of language was seen only in one patient. **Discussion** Consistent with the pattern of activation in healthy controls, patients with DA showed left lateralisation of language function, although this was weaker than the activation in healthy controls' left hemisphere. This pattern of results suggests that early bilateral hippocampal damage that reportedly alters the functional organisation of the autobiographical retrieval system, does not substantially modify the lateralisation of the speech and language network, thereby providing further evidence for the distinct functions of the two systems in relation to their neural substrates.

Disclosures: S.M. Buck: None. **T. Baldeweg:** None. **R. Elward:** None. **D. Carmichael:** None. **F. Vargha-Khadem:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.08/III63

Topic: H.02. Human Cognition and Behavior

Title: Linguistic skills and brain electrical activity during auditory processing in typically developing children

Authors: *V. V. MORALES- GARCÍA, I. G. GALÁN LÓPEZ
UNAM, Mexico City, Mexico

Abstract: Understanding the neural basis of language processing helps characterize normal functioning in typically developing children and allows early identification of developmental delays.
Only few studies have characterized normal language development by means of the association between linguistic skills and brain electrical activity. The aim of this study was to explore this relationship.
Methods
Sixty healthy Spanish native speakers aged 5-7 living in Mexico City, with Full-Scale IQ scores ranging 80-120 (obtained from WISC-IV) were recruited.
Language skills comprising auditory perception, comprehension, repetition, oral expression and metalinguistic performance, were assessed using "ENI" battery. EEG activity was recorded by 16 electrodes placed according to the International 10-20 system during two conditions: resting state (RS), where children remained calmed for 3 min, and auditory stimulation (AS), composed by 8 blocks of 15 repetitions of the monosyllable /ta/. The FFT was applied on 1s epochs to obtain absolute power (AP) of theta (θ 4-8Hz), alpha (α 8-13Hz), and beta (β 13-30Hz). AP mean of each electrode was compared between the two conditions to measure changes in brain oscillations during AS. To identify hemispheric differences in AP, electrodes were clustered into two regions (left vs right) and the mean was compared. This was done for both conditions. Correlation analysis was made between language skills and the difference in AP obtained when comparing both conditions.
Results
Twelve boys and 8 girls (mean age: 6.35 years) were included.
A significant increase in AP for θ and α bands was seen in almost every electrode site during AS. Concerning β band, only O2 exhibited a significant increase.
Left hemisphere showed significantly greater θ AP in the RS condition. No other significant difference was observed during inter-hemispheric comparison.
Negative correlations were found between θ AP and linguistic skills. Both α and β power exhibited positive correlations between frontocentral regions and language skills.
Conclusion
The absence of significant differences between RS and AS in β band, may be explained by the lack of maturation in children concerning higher frequency bands.
Moreover, the lack of inter-hemispheric difference during AS could indicate these networks are not yet completely specialized.
Negative correlations in θ band suggest lower efficiency in linguistic skills when AP increases. A decrease in slow activity is expected in normal maturation process, however children of this age range still show high values in θ band.
An increase in fast activity was also present and positively related to successful language skill performance.

Disclosures: V.V. Morales- García: None. **I.G. Galán López:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.09/III64

Topic: H.02. Human Cognition and Behavior

Support: Cognitive Science Research Initiative, Department of Science and Technology
CSIR-UGC
NBRC core grant

Title: A novel long noncoding RNA essential for human neural progenitors cells differentiation links two pathways of inherited dyslexia

Authors: *B. PRAJAPATI[1], M. FATIMA[1], M. FATMA[1], R. MIDHA[1], S. DEVASENAPATHY[1], T. NASKAR[1], R. KUMARI[2], M. MUKERJI[2], M. FARUQ[2], N. SINGH[1], P. SETH[1], S. SINHA[1,3]
[1]Natl. Brain Res. Ctr., Gurugram, India; [2]Inst. of Genomics & Integrative Biol., New Delhi, India; [3]All India Inst. of Med. Sci., New Delhi, India

Abstract: Dyslexia is a neurodevelopmental disorder with a strong familial component and complex and heterogeneous inheritance. 38 members of a large, affected multigenerational family from an endogamous group were subject to exome sequencing and validation. We identified the homozygous recessive association of a dinucleotide GT insertion at 5p15, in the 5' overlapping region of two genes transcribed in opposite directions - a novel brain expressed lncRNA LOC285696 (referred as BASP1-AU1) and BASP1. Neuronal differentiation of human Neural Progenitor Cells (hNPCs), resulted in lncRNA and BASP1 showing an initial increase followed by a sharp decline. Knockdown reduced BASP1 RNA and impaired the neural differentiation of hNPCs. BASP1-AU1 RNA, BASP1 gene, and a transcription factor TCF12 formed a molecular complex. TCF12 is located in the DYX1 locus that has been earlier extensively replicated in inherited dyslexia. Knocking down either BASP1 or TCF12 also abrogated hNPC differentiation and affected a set of genes common to BASP1-AU1 knockdown. The functions of the two distinct loci for inherited dyslexia converge during hNPC differentiation via the novel lncRNA and its interacting partners.

Disclosures: B. Prajapati: None. **M. Fatima:** None. **M. Fatma:** None. **R. Midha:** None. **S. Devasenapathy:** None. **T. Naskar:** None. **R. Kumari:** None. **M. Mukerji:** None. **M. Faruq:** None. **N. Singh:** None. **P. Seth:** None. **S. Sinha:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.10/III65

Topic: H.02. Human Cognition and Behavior

Title: Functional connectivity in Portuguese-English bilingual-biliterate adolescents without and with developmental dyslexia: Studying the role of orthographic depth

Authors: *E. BRIGNONI-PEREZ[1], A. FAY[2], N. BIANCHINI[2], A. BUCHWEITZ[2]
[1]Georgetown Univ., Washington, DC; [2]PUCRS, Porto Alegre, Brazil

Abstract: More than half of the world's population is bilingual-biliterate; however, there is a paucity of research on bilingual development, especially on the neural bases of reading, limiting our understanding of the brain's functional organization subserving successful biliteracy. Critically, there has been minimal attempt to extend the findings on the brain bases for word reading in monolingual children with developmental dyslexia (DD) to bilingual children with DD. Reading involves the coordination of numerous neurobiological mechanisms to produce fluent letter-to-sound mapping (or grapheme-to-phoneme conversion, GPC), resulting in accurate and fluent whole word reading. The functional brain system for reading in typical monolinguals, predominantly English speakers, has been exhaustively studied using functional magnetic resonance imaging (fMRI). These studies led to a prominent model that designates left-hemisphere temporo-parietal cortex (TPC) for GPC, occipito-temporal cortex (OTC) for orthographic (letter/word) processing, and inferior frontal cortex (IFC) for semantic and phonological processing. Although seen as the quintessential brain model for reading, it is limited in generalizability to all readers. It has proved to be modulated by multiple factors, including orthographic depth (OD) (i.e., the consistency of GPC). However, the specific effect of OD on brain function in bilingual children without and with DD is unknown. Previous studies have focused on detection of the different activating regions related to the written language's orthographic depth. It is critical, however, to understand how OD modulates the brain system for reading at the network level, since it is a system of intercommunicated regions rather than isolated regions working independently. We tested whether word reading in a semi-deep (Portuguese) versus a deep (English) alphabetic orthography relies on different functional connectivity between Portuguese-English bilingual-biliterate adolescents without (i.e., typically developing, TD) and with DD. Performing a seed-to-voxel approach, we found that word reading in Portuguese relies on greater correlation between regions in OTC and IFC in the TD group, and none in the DD group. Contrastingly, word reading in English relies on greater correlation between regions in OTC and TPC in the TD group, and greater correlation between regions in TPC and IFC in the DD group. Together, to our knowledge, these findings are the first evidence

showing an interaction effect between orthographic depth (semi-deep versus deep) and reading development (typical versus non-typical).

Disclosures: A. Fay: None. **N. Bianchini:** None. **A. Buchweitz:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.11/III66

Topic: H.02. Human Cognition and Behavior

Support: ChildBrain (Marie Curie Innovative Training Networks, no. 641652)
Predictable (Marie Curie Innovative Training Networks, no. 641858)
Academy of Finland (MultiLeTe #292466)

Title: Brain responses to letters and speech sounds and their correlations with cognitive skills related to reading in children

Authors: *W. XU[1,2], S. P. MONTO[1,2], O. B. KOLOZSVÁRI[1,2], J. A. HÄMÄLÄINEN[1,2]
[1]Dept. of Psychology, Univ. of Jyväskylä, Jyväskylä, Finland; [2]Ctr. for Interdisciplinary Brain Res., Jyväskylä, Finland

Abstract: Letter-speech sound (LSS) integration is crucial for initial stages of reading acquisition. However, the cortical organization for supporting LSS integration and its relationship with reading skills and cognitive skills underlying reading in early readers remain unclear. In the present study, we measured brain responses to Finnish letters and speech sounds from 29 (6-11 years, mean age 8.17 years, SD: 1.05 years, 19 girls, 10 boys) typically developing Finnish children in a child-friendly audiovisual integration experiment using magnetoencephalography (MEG). Cortically-constrained and depth-weighted L2 minimum-norm estimate (wMNE) was used for the MEG source analysis. Brain source activations in response to auditory, visual and audiovisual stimuli as well as audiovisual integration response were correlated with cognitive skills predictive of reading development and reading skills after controlling for the effect of age. Regression analysis showed that out of all the brain measures, the auditory late response around 400 ms showed the largest association with phonological processing and rapid automatized naming (RAN) abilities. In addition, the audiovisual integration effect, as revealed by cluster-based permutation test, was most pronounced in the left and right temporoparietal regions and the activities in several of these temporoparietal regions correlated with reading and writing skills. Our findings indicated the important role of temporoparietal regions in the early phase of learning to read and their unique contribution to reading skills.

Disclosures: W. Xu: None. **S.P. Monto:** None. **O.B. Kolozsvári:** None. **J.A. Hämäläinen:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.12/III67

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS-1551330

Title: Neurobiological underpinnings of rapid white matter plasticity during intensive reading instruction

Authors: *E. HUBER, J. YEATMAN
Psychology, Univ. of Washington, Seattle, WA

Abstract: Experience can modify the microstructure of the white matter over remarkably short timescales. The majority of past work examining white matter plasticity in humans has relied on metrics derived from diffusion MRI (dMRI) and the diffusion tensor model, which can be influenced by several distinct biological properties of the white matter. Broadly, these properties can be characterized as features of axons, such as their caliber, packing density, coherence, and myelination, or features of the extra-axonal space, such as the number and/or size of glial cells, and constituents of the extracellular matrix. Here we use diffusion kurtosis imaging (DKI; Jensen et al., 2005) and a biophysical model (white matter tract integrity, WMTI; Fieremans et al., 2010, 2011) to test whether microstructural changes during an 8-week, intensive reading intervention are best interpreted as rapid, experience-dependent changes in myelination, or as changes to the extra-axonal space. Behavioral measures and multi-shell dMRI data were collected at regular intervals during the intervention in a group of 32 children, ranging in age from 7-12 years. In the intervention group, but not in a group of age-matched controls, we observed large-scale changes in mean diffusivity throughout a distributed system of white matter tracts. We then examined axon water fraction and the extra-axonal axial and radial diffusivities derived from the WMTI model in the same anatomical pathways. Extra-axonal radial, but not axial, diffusivity was reduced in a large collection of tracts, including but not limited to those considered to be part of the ‘core reading circuitry’ (Vandermosten et al., 2012; Yeatman et al., 2013). AWF remained stable throughout the intervention. Although extra-axonal radial diffusivity can be impacted by myelination, a large change in myelin would also be expected to alter axon water fraction, by reducing the volume of the extra-axonal space. We therefore conclude that the rapid and widespread changes occurring in the white matter during learning are likely to reflect changes in the composition of the extra-axonal space, including changes in the size or distribution of glial cells.

Disclosures: E. Huber: None. **J. Yeatman:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.13/III68

Topic: H.02. Human Cognition and Behavior

Support: Arizona State University

Title: Exploring the link between age-related hearing loss, resting-state network connectivity, and speech comprehension in older adults

Authors: *M. C. FITZHUGH[1], L. C. BAXTER[2], C. ROGALSKY[1]
[1]Speech and Hearing Sci., Arizona State Univ., Tempe, AZ; [2]Neuroimaging Res., Barrow Neurolog. Inst. and St. Joseph's Hosp. and Med. Ctr., Phoenix, AZ

Abstract: As many as one-third of older adults without dementia experience communication difficulties that are not fully explained by hearing loss. Research suggests that as we age, the typical frontotemporal language network may not be sufficient for everyday speech comprehension, thereby requiring additional domain-general resources. The present study uses resting-state fMRI to examine how hearing loss and functional connectivity of domain-general brain networks are related to sentence comprehension in older adults. Twenty participants (60-80 years old, native English-speaking, right-handed, without cognitive impairment) completed a sentence-picture matching task, resting-state fMRI, and pure tone audiometry. The sentences varied by structural complexity (canonical and noncanonical) and background noise (multispeaker babble, broadband noise, and silence). The CONN Toolbox and SPM12 were used to compute 1) average functional connectivity between networks of interest (frontoparietal, salience, default mode, dorsal attention, and language networks) and 2) network functional connectivity correlated with participants' hearing ability. Multiple regression models were used to determine the relationship between functional connectivity measures and sentence comprehension performance in each condition. Age, vocabulary, and processing speed measures were included in the models as covariates. Results include: 1) reaction time to sentences in multispeaker babble was significantly positively correlated with functional connectivity between the portions of the salience and language networks; reaction time for noncanonical sentences was significantly positively correlated with the functional connectivity between the frontoparietal and language networks. 2) Poorer hearing correlated with reduced connectivity between the salience network and portions of the default, dorsal attention, and language networks. These functional connectivity reductions did not significantly predict reaction time in any sentence comprehension condition. These initial results suggest that that increased effort during sentence comprehension (i.e. longer reaction times) in older adults is not explained by network changes related to hearing

loss, but instead may be related to greater network connectivity between the language network and specific domain-general networks. It also is noteworthy that the background noise and structural complexity manipulations of sentence difficulty are differentially taxing the frontoparietal and salience networks.

Disclosures: M.C. Fitzhugh: None. **L.C. Baxter:** None. **C. Rogalsky:** None.

Poster

696. Human Cognition and Behavior: Language Developmental Processes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 696.14/JJJ1

Topic: H.02. Human Cognition and Behavior

Support: NSFC 31571158

Title: Aging modulates the effects of cognitive demands on brain-wide network architectures

Authors: *Q. ZHOU, L. LIU, H. LI, Y. ZHANG, C. LU, G. DING
Beijing Normal Univ., Beijing, China

Abstract: **Introduction**: Several studies have shown that aging affects brain-wide network properties at rest (Geerligs et al., 2015) and during cognitive tasks (Sheppard et al., 2011). It is also reported that task-related brain architectures differ from the intrinsic brain architectures in terms of connectivity patterns and network topology (Bolt et al., 2017), suggesting the brain network is modulated by cognitive demands. However, it is still unclear whether and how the modulation of cognitive demands on brain network changes along aging. **Methods**: In the current study, we used functional magnetic resonance imaging (fMRI) technique to record the brain activities when 26 young (12F, age = 20.23) and 25 old (14F, age = 64.20) participants performed a spoken word comprehension task (Task-on), which alternated with a baseline block of passively viewing a scrambled picture (Task-off), and when at rest (resting state). The three different states require decreasing cognitive demands. Brain activation was first analyzed and compared between the two groups. Then graph theoretical analyses were conducted with a whole-brain atlas (Power et al., 2011). Several global metrics (global efficiency, local efficiency, small-world, and modularity) were computed, and repeated-measures ANOVA was performed. We repeated this analysis over a range of sparsity thresholds (from 0.1 to 0.16) and computed the area under the curve (AUC) for each network. **Results**: Behavior results show that young adults have better performance on the spoken word comprehension task than old adults, with higher accuracy and shorter reaction time. Interestingly, brain activation analysis doesn't show any differences between the two groups. However, group differences are found in the graph analysis. To be brief, here we only present the result of the AUC, which is representative of each sparsity. For the global efficiency, we only find a significant main effect of group. While for the other

three indexes, the results show significant main effects of states and group and also the interaction between them. The simple effects analysis of network properties further revealed that young group shows no difference between the task-on and task-off condition, but old group shows significant decline in these three indexes from the task-off state to task-on state. Resting-state network shows a trend that it has higher network properties than the other two states in both groups. **Conclusion**: Our graph theory analysis reveals that the characteristics of whole brain network of older adults change enormously with different cognitive demands while those of young adults could almost keep stable across the three states.

Disclosures: Q. Zhou: None. **L. Liu:** None. **H. Li:** None. **Y. Zhang:** None. **C. Lu:** None. **G. Ding:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.01/JJJ2

Topic: H.02. Human Cognition and Behavior

Title: Theta phase sychrony in a spatial cognitive control network

Authors: *L. K. CHINN[1], J. MYERS[2], E. J. GOLOB[2]
[1]Tulane Univ., New Orleans, LA; [2]Univ. of Texas At San Antonio, San Antonio, TX

Abstract: Direct recordings from the anterior cingulate cortex (ACC) in primates suggest that theta oscillations (3-8 Hz) increase power during the control of attention. Measured with EEG in humans, frontal midline theta power also increases during cognitive control, supporting evidence that neurons in this area synchronize during cognitive control. Although the ACC is thought to be a major source of cognitive control in the brain, less is known about how it communicates with other regions on a millisecond basis to form the functional connectivity underlying cognitive control. To address this question, we measured neural coherence (i.e., phase synchrony) during an auditory Simon task where subjects (N = 47) pressed a left or right button in response to sounds on each trial to indicate which of the two possible sounds were presented. On half of trials, the sounds were presented in the earphone ipsilateral to the correct response (i.e., compatible trials). For the other half of trials, the sound was presented contralateral to the correct response, leading to stimulus-response conflict (i.e., incompatible trials). Theta coherence was measured between independent components localized near the ACC, primary motor, and superior parietal lobe in each subject. Results indicated that theta coherence between dorsal and ventral ACC was highest when an incompatible trial was preceded by a compatible trial ($p < 0.001$, $\eta^2 = 0.297$). Compatible-then-incompatible trial sequences have been shown to maximize stimulus-response conflict, thus requiring more cognitive control than other sequence conditions.

During the average behavioral response time (350-550 ms), theta coherence also increased between the dorsal ACC and the primary motor cortex, suggesting that the ACC might communicate conflict information to motor regions in order to avoid errors ($p = 0.008$, $\eta^2 = 0.190$). Coherence between the dorsal ACC and the right superior parietal lobe also maximized for compatible-then-incompatible sequences, but was minimal when both the current and previous trials were compatible ($p = 0.006$, $\eta^2 = 0.176$). Results provide evidence that the ACC is part of a sensorimotor and attentional network that appraises stimulus input to optimize selection of correct behavioral responses during cognitive control.

Disclosures: L.K. Chinn: None. **J. Myers:** None. **E.J. Golob:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.02/JJJ3

Topic: H.02. Human Cognition and Behavior

Support: Simons Foundation 543015SPI
NIMH grant P50MH094258
NSF CAREER grant 1554105

Title: Phase-locking of neurons in human medial frontal cortex to hippocampal theta is engaged by declarative memory-based decisions

Authors: *J. MINXHA[1], R. ADOLPHS[1], A. MAMELAK[2], U. RUTISHAUSER[3]
[1]Caltech, Pasadena, CA; [2]Cedars Sinai, Los Angeles, CA; [3]Dept. of Neurosurg., Cedars-Sinai Med. Ctr., Los Angeles, CA

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 semantic knowledge). We recorded from 360 neurons in amygdala and hippocampus (MTL), and 399 neurons in dorsal anterior cingulate cortex and pre-supplementary motor area (MFC) in nine 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). In MFC, we identified 78 cells that signaled the choice made (yes or no) only on the memory (n=40/78), the categorization (n=29/78), or both trials (n=9/78), but invariant to the type of choice action (button press or saccade) and not coding motor response (as a control, we also asked subjects to respond with a

button press or a saccade). MFC cells that encoded memory-based choices showed strong modulation of their spike-field coherence with local field potentials in the theta range 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. A further lag analysis of spike-field coherence between the two areas revealed that MTL theta leads (i.e. entrains) spiking activity in the MFC. These results support a model according to which memory representations are conveyed from the MTL to the MFC, dynamically routed as a function of the demands of the task, and that specific neuronal populations within the MFC may then abstract category membership from such memory representations.

Disclosures: J. Minxha: None. **R. Adolphs:** None. **A. Mamelak:** None. **U. Rutishauser:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.03/JJJ4

Topic: H.02. Human Cognition and Behavior

Support: NEDO (15102349-0)
KAKENHI (18H03142)

Title: Neural representation of the target selection “to buy” in the human EEG

Authors: *H. SAWAHATA, Y. NAKAMURA, R. P. HASEGAWA
Human Informatics Res. Inst., AIST, Tsukuba, Japan

Abstract: Neuromarketing is expected to reveal the neural basis of the decision-making processes of consumers that reflect both a conscious and unconscious intentions to purchase products. It is, however, still unclear how such an intention is represented by brain activity. In this study, we used our custom-made BMI system, the Neurocommunicator® to record EEG activities from the normal subjects (n=12) during a cognitive task as a model of shopping behavior in order to explore the neural indicator of the intention to buy. The task was based on the sequential delayed matching-to-sample paradigm, in which the subject looked for one of eight visual stimuli (pictures of products such as chair, cake, dress, etc.). EEG signals were recorded from 8 electrodes around the top of the head (FC1, FC2, C3, Cz, C4, CP1, CP2, and Pz)

while subjects silently counted the times of presentations of the product ('target to buy') that the subjects most wanted to buy out of 8 products in a group. As a control, we also tested the subjects the same task except that the target was the product ('target NOT to buy'), which they never wanted to buy. As the results, we observed the greater event-related potentials (ERPs) responded to the target than that to the nontarget in both 'to buy' and 'NOT to buy' conditions, replicating the previous studies. The magnitude of the response to the 'target to buy' was, however, greater than that to the 'target NOT to buy' especially during the period of 250-550 ms after stimulus onset. Such an enhanced response to the 'target to buy' around the similar period was also observed by the short-time Fourier transformation method. In fact, the power to the 'target to buy' was more increased than that to the 'target NOT to buy' in the low-gamma frequency band (32-48 Hz). These results suggest that strong ERP response and large low-gamma power become a candidate of the neural indicator of the purchasing intention, which could be useful not only for a neuromarketing tool but also an EEG-based shopping aid of patients with severe motor deficits.

Disclosures: H. Sawahata: None. **Y. Nakamura:** None. **R.P. Hasegawa:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.04/JJJ5

Topic: H.02. Human Cognition and Behavior

Title: Electrophysiological and hemodynamic correlates of self-committed and observed decision monitoring

Authors: *M. PEREIRA, N. FAIVRE, I. ITURRATE, L. SERAFINI, S. MARTIN, A. DESVACHEZ, O. BLANKE, M. WIRTHLIN, D. VAN DE VILLE, J. DEL R. MILLÁN
Ecole Polytechnique Fédérale de Lausanne (EPFL), Geneva, Switzerland

Abstract: Humans can monitor their own mental lives and build knowledge about themselves. This capacity to introspect and report one's own mental states, or in other words "knowing how much one knows", is termed metacognition. Here, we assessed the contribution of motor signals to metacognition by identifying the behavioral and neural correlates for monitoring self-committed vs. observed decisions. We recruited twenty healthy volunteers for a simultaneous EEG-fMRI experiment, in which they had to decide which of two stimuli contained the more dots by pressing a key (first-order task, active condition), or to observe the computer deciding for them (observation condition). Subsequently, they had to indicate their confidence in the choice made (second-order response). Metacognitive performance, defined as the extent to which confidence tracks first-order performance, was better in the active compared to the observation

condition, indicating that the monitoring of motor actions occurring in the active condition improved the sense of confidence. During the active condition, EEG over the parietal and frontal midline of the scalp predicted confidence as early as 100 ms after the response, while in the observation condition this prediction was shifted in time to around 350 ms after the observation of the response. We then used the single-trial EEG predictions of confidence as parametrical regressors to model the blood-oxygen-level dependent (BOLD) signal. We found that for the active condition, early EEG correlates of confidence (between 50 and 250 ms after the response) were explained by supplementary motor area and inferior frontal gyrus BOLD activations. In both conditions, late EEG correlates (250 to 450 ms) were explained by supplementary motor area and inferior parietal BOLD activations. Interestingly, Fronto-polar (BA10) regions better explained late EEG activity in the active than in the observation condition. Based on these results, we discuss how the computation of confidence may be grounded onto action monitoring, in line with recent theoretical frameworks suggesting that predictions about bodily signals shape cognition.

Disclosures: M. Pereira: None. **N. Faivre:** None. **I. Iturrate:** None. **L. Serafini:** None. **S. Martin:** None. **A. Desvachez:** None. **O. Blanke:** None. **M. Wirthlin:** None. **D. Van De Ville:** None. **J. del R. Millán:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.05/JJJ6

Topic: H.02. Human Cognition and Behavior

Support: ERC Grant 63829 (to R.G.O)

Title: Neurophysiological underpinnings of the diminished capacity for regulating speed-accuracy tradeoffs in older age

Authors: *J. DULLY[1], G. LOUGHNANE[2], S. KELLY[3], R. G. O'CONNELL[4]
[1]Trinity Col. Inst. of Neurosci., Dublin, Ireland; [2]Trinity Col., Dublin, Ireland; [3]Sch. of Electrical and Electronic Engin., Univ. Col. Dublin, Dublin, Ireland; [4]Trinity Col. Dublin, Dublin, Ireland

Abstract: The ability to adjust decision making strategies to account for changing demands for speed versus accuracy is an essential component of adaptive choice behaviour. It has consistently been observed that older adults have diminished flexibility in this regard but it is unclear how this manifests in neural signatures of decision formation. In the present experiment, healthy older adults (65 - 80 years) and younger adults (18 - 35 years) engaged in a two-alternative contrast discrimination task (n = 60), consisting of discrete trials featuring two superimposed

leftward/rightward gratings which gradually changed in relative contrast. Stimuli were presented under two conditions emphasising accuracy versus speed, imposed via verbal instruction to participants as well as feedback in the form of points. Instructions to switch between tasks were given on a block-by-block basis. Continuous 128-channel EEG data were also recorded, to allow for probing of the distinct stages of the sensorimotor hierarchy (sensory encoding, evidence accumulation, and motor preparation). In keeping with the findings of previous studies, older adults were less amenable to speed accuracy manipulations at the behavioural level. Although the age groups were matched for accuracy and reaction time when accuracy was emphasised, the reaction times of older adults were significantly slower than those of younger adults when speed was emphasised and consequently earned fewer points in this regime. Analysis of beta band activity indicated that this effect was at least partly attributable to differences in the adjustments that were made at the level of motor preparation. While young participants exhibited markedly greater motor preparation at trial onset under speed compared to accuracy emphasis, this modulation was less pronounced among the older adults. However, further neurophysiological analyses highlighted a number of additional age-related effects manifesting at other processing levels. Older adults exhibited stronger sensory evidence encoding signals (Steady State Visual Evoked Potentials), with an accordingly faster build-up of evidence accumulation, indexed by the centro-parietal positivity (CPP). These compensatory mechanisms may account for the comparable accuracy across age groups. These results add insight to performance differences between younger and older adults, and contribute to our understanding of the limitations faced by older adults in the domain of decision making.

Disclosures: J. Dully: None. **G. Loughnane:** None. **S. Kelly:** None. **R.G. O'Connell:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.06/JJJ7

Topic: H.02. Human Cognition and Behavior

Title: Cortical electroencephalographic activity in the different phases of decision-making

Authors: *J. P. GARCÍA HERNÁNDEZ[1,2], P. M. CORTES-ESPARZA[2], M. L. RAMÍREZ-RENTERÍA[2], M. A. GUEVARA[2], M. HERNANDEZ-GONZÁLEZ[2]
[1]Inst. de Neurociencias, Guadalajara, Mexico; [2]Inst. de Neurociencias, Univ. de Guadalajara, Guadalajara, Mexico

Abstract: Decision-making has been divided into 3 stages based on distinct functionalities, as follows: 1) forming preferences; 2) executing action(s); and 3) experiencing the outcome. This division also has a basis in the different cerebral structures involved in each stage. Among the

areas involved in the different phases, the parietal and frontopolar cortices participate in evaluating the stimuli and the perception-action cycle that is required to correctly perform decision-making. Against this background, the objective of this study was to characterize the electrical activity of the parietal and frontopolar cortices during the different phases of decision-making. Subjects in this study were 30 healthy, right-handed men aged 20-35. Electroencephalographic activity (EEG) was recorded from the frontopolar (Fp1-Fp2) and parietal (P3-P4) cortices during phases 1, 2 and 3 of a decision-making task. Absolute power (AP) as well as interhemispheric EEG (Fp1-Fp2 and P3-P4) and intrahemispheric EEG (Fp1-P3 and Fp2-P4) correlations were analyzed in the following EEG bands: delta (1-3.5 Hz), theta (4-7.75) Hz), alpha1 (8-10.5 Hz), alpha2 (11-13.5 Hz), beta1 (14-19.5 Hz), beta2 (20-30 Hz) and gamma (31-50 Hz). A lower AP of the alpha1 and alpha2 bands was observed in frontopolar areas during stage 2, whereas during stage 3, a higher AP in the delta and theta bands was obtained with respect to the other two stages. In parietal areas, a higher AP in the slow bands (delta and theta) and a lower AP in the fast bands were obtained in stage 2 compared to stages 1 and 3. During stage 2, the degree of interhemispheric EEG synchronization between areas Fp1-Fp2 showed a lower EEG correlation from the delta to beta1 bands, but a higher correlation in the gamma band, compared to stages 1 and 3. Also in stage 2, a higher correlation from the theta to gamma bands was obtained between areas P3-P4. The intrahemispheric EEG correlation showed a decrease in the delta, beta1, beta2 and gamma bands in stage 2, with respect to the other stages. These EEG data
show that the activation and degree of functional coupling between the parietal and frontopolar cortices change during the decision-making process. Taken together, our findings suggest that frontopolar activity is related to the adequate stimuli-processing phase, while the parietal cortex is involved primarily in the action-execution components of decision-making.

Disclosures: J.P. García Hernández: None. **P.M. Cortes-Esparza:** None. **M.L. Ramírez-Rentería:** None. **M.A. Guevara:** None. **M. Hernandez-González:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.07/JJJ8

Topic: H.02. Human Cognition and Behavior

Support: Australian Research Council FT130101488
Australian Research Council DP150100986

Title: Integrated analysis of EEG and MRI data reveals critical role of dorsal attention network in human evidence accumulation

Authors: *M. BROSNAN[1], T. SILK[4], K. SABAROEDIN[2], S. GENE[5], D. P. NEWMAN[2], G. LOUGHNANE[6], A. FORNITO[7], R. G. O'CONNELL[8], M. A. BELLGROVE[3]
[1]Monash Inst. of Cognitive and Clin. Neurosciences, Monash Univ., Clayton Melbourne, Australia; [2]Monash Univ., Melbourne, Australia; [3]Monash Univ., Clayton, Australia; [4]Murdoch Children's Res. Inst., Melbourne, Australia; [5]Murdoch Children's Res. Inst., Melbourne, Australia; [6]Trinity Col., Dublin, Ireland; [7]Monash Clin. and Imaging Neurosci., Clayton, Australia; [8]Trinity Col. Dublin, Dublin, Ireland

Abstract: Electrophysiological recordings from rodents, monkeys and humans have demonstrated that decisions are formed by accumulating sensory evidence up to an action-triggering bound. Evidence accumulation signals have been identified in several fronto-parietal regions governing visual attention & premotor processes, yet it is unclear how decision-relevant information is efficiently communicated across these separate areas to facilitate speeded perceptual reports. Here, neural metrics of evidence accumulation were isolated in human participants using EEG, and related to both diffusion and resting state (rs)-MRI. The rate of evidence accumulation mediated the relationship between white matter structural organisation of the dorsal branch of the superior longitudinal fasciculus (projecting to the dorsal attention network; DAN), and the speed of perceptual reports. rs-MRI analyses confirmed that faster rates of evidence accumulation were related to stronger premotor-DAN connectivity. These results demonstrate that connectivity within the DAN influences interindividual variability in the rate of human evidence accumulation.

Disclosures: M. Brosnan: None. **T. Silk:** None. **K. Sabaroedin:** None. **S. Gene:** None. **D.P. Newman:** None. **G. Loughnane:** None. **A. Fornito:** None. **R.G. O'Connell:** None. **M.A. Bellgrove:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.08/JJJ9

Topic: H.02. Human Cognition and Behavior

Support: H2020 European Research Council (670325)
École des Neurosciences de Paris Ile-de-France
ANR-10-IDEX-0001-02 PSL*
ANR-10-LABX-0087 IEC

Title: Neural responses to heartbeats impact value encoding in subjective, preference-based decision-making in ventro-medial prefrontal cortex

Authors: *D. C. AZZALINI, S. PALMINTERI, C. TALLON-BAUDRY
Dept. d'études cognitives, Lab. de Neurosciences Cognitives, École Normale Supérieure, Paris, France

Abstract: Preference-based decisions rely on subjective values: whether you prefer wine or beer is solely determined by your own experience, and this preference is only accessible to you. In the field of decision-making, the subjective status of preferences has not been highlighted thus far. On the other hand, subjectivity has been a long-standing issue in consciousness research. Neural responses to heartbeats (aka heartbeat evoked responses) have been recently proposed as a candidate mechanism to generate a self-centered reference frame to which subjective processes would be bound. Here, we tested whether neural responses to heartbeats distinguish decisions that are based on internally generated evidence - hence self-centered - from those based on external evidence.
21 healthy human participants performed preference-based and perceptual choices on pairs of movie titles while their brain and cardiac activities were recorded with magneto-encephalography (MEG) and electrocardiography (ECG), respectively. The type of decision to be performed was indicated at the beginning of each trial by a geometrical cue (a square or a diamond) presented on the screen for a fixed delay of 1.5 s. After the cue, two movie titles of slightly different luminance were displayed on a light gray background. In preference-based choices, subjects had to indicate which movie they liked more, whereas in perceptual choices, which title looked darker. After response and a variable delay, the next trial began. The exact same pairs of titles were presented twice, once per decision type.
Our results show that, during cue presentation (hence, before options are displayed), neural responses to heartbeats in the rostral part of vmPFC are larger when subjects have to prepare for preference judgment as compared to perceptual choice. During option presentation, the chosen value in preference decisions is encoded in caudal vmPFC, in agreement with the fMRI literature. Our analyses further reveal that value encoding in caudal vmPFC is enhanced for trials in which neural responses to heartbeats during task preparation are larger. On the contrary, in perceptual decisions, the luminance value of the chosen title is encoded in a posterior network of brain regions, and is not modulated by the amplitude of neural responses to heartbeats.
We thus show here that preparing for a preference-based judgment enhances responses to heartbeats in (rostral) vmPFC, and that those responses to heartbeats modulate the strength of subsequent subjective value encoding in (caudal) vmPFC.

Disclosures: D.C. Azzalini: None. **S. Palminteri:** None. **C. Tallon-Baudry:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.09/JJJ10

Topic: H.02. Human Cognition and Behavior

Title: STN-DBS, not L-DOPA, restores the contextual regulation of perceptual decisions

Authors: *L. J. RONDOT[1], M. ULLA[2,3], V. WYART[4], J.-J. LEMAIRE[2,5], J.-C. DREHER[6], F. DURIF[2], P. DOMENECH[1,7]
[1]Inst. du Cerveau et de la Moelle, Paris, France; [2]Neurol., Univ. Hosp. of Clermont-Ferrand, Clermont-Ferrand, France; [3]Vigimed Med. Ctr., Martigny, Switzerland; [4]Lab. de Neurosciences Cognitives, Dept. d'Etudes Cognitives, ENS, Paris, France; [5]Image-Guided Clin. Neurosci. and Connectomics, Auvergne Univ., Clermont-Ferrand, France; [6]Neuroeconomics, Reward and Decision-making, Inst. des Sci. Cognitives Marc Jeannerod, CNRS, Bron, France; [7]DHU PePSY, Dept. of Functional Neurosurg. and Psychiatry, Henri Mondor Hosp. (AP-HP), Créteil, France

Abstract: Perceptual decision-making can be described as a process by which sensory evidence is accumulated until a decision threshold (DT) is reached. This DT is adaptively tuned to its context, such as the probabilistic regularities of the environment. Here, we consider two types of contextual information: (1) the predictive information (PI), which is the log probability ratio of an event occurring given a previous event, relative to its frequency and (2) the contextual uncertainty (CU) which is the prior entropy over an events' occurrence given a previous event. This study aims at specifying how patients suffering from Parkinson's disorder (PD patients) adjust their DT to contextual information compared to healthy matched controls (HC) and how does levodopa (L-DOPA) treatment affect this adjustment compared to deep-brain stimulation of the subthalamic nucleus (STN-DBS).
14 PD patients performed a simple perceptual decision making task under 4 pseudo-randomly ordered conditions: ON or OFF L-DOPA treatment and ON or OFF STN-DBS. 31 HC subjects also performed the task once. In the task, the subjects pressed a button to match the shape presented on screen. Transitions between shapes were controlled to systematically manipulate contextual information. The electroencephalography of patients was also recorded in each condition.
L-DOPA reduced both PD patient's RTs (F (11) = 129.73, $p < .0001$) and performance (F (11) = 7574.2, $p < .0001$), suggesting a shift in the speed-accuracy trade-off. This deleterious effect was significantly limited with STN-DBS, both in RTs (F (11) = 101.75, $p < .0001$) and performances (F (11) = 8201.5, $p < .0001$). RTs in HC decreased with PI (Z = 4.076, $p < .0001$) and increased with CU (Z = - 4.292, $p < .0001$). There was no significant effect of PI nor of CU on RTs of untreated patients. The effects of both PI (Z = 2.746, p = .006) and CU (Z = - 2.275 ; p = .023) on RTs was restored when patients were OFF L-DOPA + ON STN-DBS and there was no significant difference in the effects compared to HCs.
These preliminary behavioural results suggest that L-DOPA treatment has a deleterious effect on simple perceptual decisions causing a shift of the speed-accuracy trade-off toward impulsivity, which is somewhat rectified by STN-DBS. Moreover, the use of contextual information (both PI and CU) is deteriorated in untreated PD patients but this impairment is fully rectified through STN-DBS, but not L-DOPA.

Disclosures: L.J. Rondot: None. **M. Ulla:** None. **V. Wyart:** None. **J. Lemaire:** None. **J. Dreher:** None. **F. Durif:** None. **P. Domenech:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.10/JJJ11

Topic: H.02. Human Cognition and Behavior

Support: Swiss National Science Foundation 00014_165884

Title: Insula processes salience prediction error for primary reinforcers

Authors: *J.-C. KIM, L. HELLRUNG, M. GRÜSCHOW, E. KAPETANIOU, A. BAGAINI, D. HINZ, P. N. TOBLER
Univ. of Zurich, Zurich, Switzerland

Abstract: Salience guides attention and accelerates behavior. In a formal definition of salience as absolute value, salience increases both when reward or punishment surprisingly occur and when they surprisingly fail to occur. Thus, even though reward occurrence and punishment absence have positive value whereas reward absence and punishment occurrence have negative value, all four outcome types commonly have higher salience than the occurrence or absence of a neutral event. In this study, we designed a novel task that controlled for the absolute value of primary reward and punishment in the form of appetitive and aversive liquids and investigated salience processing in the fMRI scanner. We individualized the liquid types and concentrations to each of the 50 participants' tastes. For example, we used fruit juices and milk drinks as rewards, saline and bitter solutions (PROP) as punishments. Distilled water with the main ionic components of saliva served as neutral liquid. Each participant performed a calibration session during which we individualized appetitive and aversive liquids and two fMRI sessions for the main task. Before starting the main task, participants learned to associate three distinct visual cues with one of three different liquids (appetitive, aversive, or neutral). For each of the three cues, liquid delivery occurred at p=0.5. In the main task, each trial started with the presentation of a visual cue. After a variable delay (mean 1.5 s), the fixation cross changed color, the participants received liquid or no liquid and rated the outcome. The absolute value of reward did not differ significantly from that of punishment ($t=1.8277$, $p=0.1182$) but was higher than that of the neutral liquid (appetitive: $t=3.2020$, $p=0.0116$; aversive: $t=2.1291$, $p=0.0773$). Preliminary analyses at the neural level suggest that the surprising absence of both appetitive and aversive liquids activated the left insula and the amygdala more than the surprising absence of neutral liquid ($p<0.001$, uncorrected). Moreover, the left insula (and to a lesser degree the amygdala) also showed stronger activation to the surprising delivery of appetitive and aversive liquids compared to neutral liquids. These data suggest that the insula processes a salience prediction error.

Disclosures: **J. Kim:** A. Employment/Salary (full or part-time):; University of Zurich. **L. Hellrung:** None. **M. Grüschow:** None. **E. Kapetaniou:** None. **A. Bagaini:** None. **D. Hinz:** None. **P.N. Tobler:** A. Employment/Salary (full or part-time):; University of Zurich.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.11/JJJ12

Topic: H.02. Human Cognition and Behavior

Support: R01 MH110311

Title: Predictive coding depends on causal inference and NMDA receptor-mediated feedback in the brain

Authors: ***S. MOHANTA**[1], D. POLYAKOV[2], M. J. REDINBAUGH[3], N. A. KAMBI[3], J. M. PHILLIPS[3], S. TANABE[2], W. FILBEY[2], J. KILDOW[2], S. TWADELL[2], J. L. AUSTERWEIL[3], R. D. SANDERS[2], Y. B. SAALMANN[3]
[2]Anesthesiol., [3]Psychology, [1]Univ. of Wisconsin, Madison, Madison, WI

Abstract: Predictive coding is the ability to make predictions about upcoming events in our sensory environment based on prior experience, allowing efficient processing of sensory input. According to this framework, predictions are sent from higher-order to sensory cortex along feedback pathways. Such feedback is often associated with neural processing in alpha/low beta frequencies. Recent evidence suggests that feedback also involves NMDA receptors. However, it is unclear if these neural mechanisms contribute to predictions.
To test mechanisms of predictive coding, we used an audio-visual learned-association task, in which subjects (n=25; 13 female) indicated whether the initial sound and subsequent image matched. Importantly, we manipulated subjects' predictions by varying the probability of an image appearing after its associated sound. We conducted a hierarchical drift-diffusion analysis of subjects' reaction times, in which the drift rate and bias depended on the evidence for a causal relation. To investigate the underlying neural processes, we recorded EEG signals using a 256-channel array. We also aimed to pharmacologically manipulate predictions, by administering sub-anesthetic doses of ketamine, an NMDA receptor blocker, or dexmedetomidine, an α2-adrenergic receptor agonist.
Subjects' reaction times were faster when sounds had greater predictive value in the audio-visual task. The hierarchical drift-diffusion analysis shows that causal inference (which accounts for how often a particular image follows its associated sound, and how often that image follows other sounds) predicted reaction times better than transitional probabilities (how often a particular image follows its associated sound only). During the delay period, prior to image

onset, occipital alpha power correlated with predictions.
Preliminary pharmacology results suggest that ketamine, but not dexmedetomidine, blocks predictions: predictive value did not influence reaction times. When we incorporated these pharmacological interventions into the drift-diffusion model, causal inference failed to predict reaction times for ketamine; but causal inference could predict reaction times for the control, dexmedetomidine. Ketamine also reduced prediction-correlated delay period alpha power in occipital electrodes.
Taken together, this suggests that predictions depend on causal inference, and not just transitional probabilities. Because NMDA receptors have been reported to contribute to feedback processes, our data are consistent with a role for NMDA
receptor-mediated feedback from higher-order to sensory cortex as a key mechanism enabling predictive coding.

Disclosures: S. Mohanta: None. **D. Polyakov:** None. **M.J. Redinbaugh:** None. **N.A. Kambi:** None. **J.M. Phillips:** None. **S. Tanabe:** None. **W. Filbey:** None. **J. Kildow:** None. **S. Twadell:** None. **J.L. Austerweil:** None. **R.D. Sanders:** None. **Y.B. Saalmann:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.12/JJJ13

Topic: H.02. Human Cognition and Behavior

Support: Clemson Creative Inquiry Program

Title: Examining the interaction between striatal dopamine and externalizing behaviors on prediction errors during decision making

Authors: *E. A. NEWELL, K. A. BYRNE
Clemson Univ., Clemson, SC

Abstract: Externalizing behaviors affect between 8-9% of Americans annually (Insel & Fenton, 2005). Two externalizing behaviors that share a common heritable liability are disinhibition and substance abuse (Krueger & Markon, 2006). Prior research suggests that genetic variation in striatal dopaminergic function contributes to general proneness to externalizing problems (e.g., Derringer et al., 2010; Krueger & Markon, 2006). Moreover, striatal tonic dopamine levels also affect phasic reward prediction error dopamine responses, which is critical to reward learning and decision-making (Cools & D'Esposito, 2011; Evers et al., 2016). Thus, dopaminergic variation is independently associated with both a general liability for externalizing behaviors and reward prediction errors. However, it is unclear how variation in striatal dopamine modulates the

relationship between externalizing behaviors and reward prediction errors during decision-making. This study investigated the interaction between striatal dopamine and externalizing behaviors on prediction errors during decision making. Participants (*N*=104) self-reported problematic substance use and disinhibition behaviors using the Externalizing Spectrum Inventory Brief Form (Patrick et al., 2013). Participants then performed a novel four-choice reward-based decision-making task in which they chose an option, estimated their expected reward, and then received feedback on the reward amount they actually earned. Striatal tonic dopamine levels were operationalized using spontaneous eye blink rate. The outcome measure, prediction errors, was computed as the average difference between the reward estimated and the reward received. Hierarchical regression results revealed main effects of substance abuse and striatal dopamine in which high striatal dopamine and higher levels of problematic substance use predicted larger magnitude negative prediction errors, and thus an overestimation of expected rewards. A significant interaction between striatal dopamine and disinhibition was also observed in which more impulsive individuals with high levels of striatal dopamine made more negative prediction errors. This suggests that variation in striatal tonic dopamine modulates the effect of disinhibitory tendencies on decision-making, which is consistent with previous work in our lab (Byrne et al., 2016). These findings underscore the importance of considering individual differences in dopaminergic functioning to determine cognitive correlates of externalizing proneness.

Disclosures: E.A. Newell: None. **K.A. Byrne:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.13/JJJ14

Topic: H.02. Human Cognition and Behavior

Support: NWO Vici award 453-14-015

Title: Does dopamine modulate the willingness to exert cognitive control?

Authors: *L. HOFMANS[1,2], D. PAPADOPETRAKI[1,2], R. VAN DEN BOSCH[1,2], J. I. M. MÄÄTTÄ[1,2], B. I. H. M. LAMBREGTS[1], A. WESTBROOK[1,2,3], R. COOLS[1,2]
[1]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ., Nijmegen, Netherlands; [2]Dept. of Psychiatry, Radboud Univ. Med. Ctr., Nijmegen, Netherlands; [3]Cognitive, Linguistics, & Psychological Sci. Dept., Brown Univ., Providence, RI

Abstract: Brain dopamine has long been implicated in working memory and cognitive control (Sawaguchi et al., 1991; Cohen et al., 2002). Moreover, dopamine is important for motivation

and decision making, as evidenced by effects of dopaminergic drugs on physical effort-based decision making (Treadway et al., 2009; Salamone et al., 2016). We aim to integrate these lines of evidence and ask whether dopamine also plays a role in cost-benefit decision making about cognitive control. To address this question, we combined PET, psychopharmacology and a cognitive effort-discounting choice procedure with a classic delayed response task of working memory. In this placebo-controlled, double-blind, cross-over design, 50 healthy participants (25 females) completed a working memory task as well as a subsequent preference task on 3 sessions: once after intake of placebo, once after a low oral dose (20mg) of the catecholamine reuptake blocker methylphenidate and once after intake of a low oral dose (400mg) of the selective dopamine receptor antagonist sulpiride. All participants also underwent an [^{18}F]DOPA PET scan to quantify their baseline dopamine synthesis capacity. This allowed us to ask whether their willingness to perform a cognitive task for reward varies with (i) individual differences in striatal dopamine synthesis capacity and (ii) dopaminergic drug administration, perhaps interacting with baseline synthesis capacity. Analyses of blinded data, collapsed across all three sessions, do not demonstrate a relationship between individual variation in dopamine levels and willingness to perform the task. However, preliminary exploratory analyses revealed an interesting pattern of results as a function of session, with willingness to perform the task declining with session, despite, if anything, increases in performance. Critically, dopamine synthesis capacity predicted the degree to which willingness to perform the task decreased from the first to the last session. Participants with higher levels of dopamine synthesis capacity exhibited a greater reduction in willingness to perform the task across sessions than did low dopamine participants, supporting a role for dopamine in cognitive effort-based decision-making (Froböse et al., 2017). We will further investigate these preliminary between-subject effects of dopamine by examining the within-subject drug effects on willingness to perform the task, as a function of baseline dopamine synthesis capacity.

Disclosures: L. Hofmans: None. **D. Papadopetraki:** None. **R. van den Bosch:** None. **J.I.M. Määttä:** None. **B.I.H.M. Lambregts:** None. **A. Westbrook:** None. **R. Cools:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.14/JJJ15

Topic: H.02. Human Cognition and Behavior

Title: Corticostriatal representation of information value during ambiguous decision-making

Authors: *U. R. KARMARKAR[1,2], S. YE[3], V. RIMEIKYTE[4], E. KASTMAN[5], J. W. BUCKHOLTZ[6]

[1]Rady Sch. of Mgmt., LA Jolla, CA; [2]Sch. of Global Policy and Strategy, UCSD, La Jolla, CA; [3]Harvard Business Sch., Cambridge, MA; [4]Human Develop., Cornell Univ., Ithaca, NY; [5]Harvard Univ., Boston, MA; [6]Harvard Univ., Cambridge, MA

Abstract: The economic definition of ambiguity refers to uncertain situations in which both the outcomes, and the probabilities of the outcomes are unknown. Thus people have to make choices with incomplete information, which is generally found to be aversive, and to have negative effects on decision-making. In this work, we focus on how people use the partial information they do have. In particular, we examine how incremental information that is favorable or unfavorable to a desired outcome influences valuation of an ambiguous financial prospect and how this information is represented in the brain. We collected behavioral and fMRI data from 34 participants who received varying levels of valenced information about financial gambles. In this "Pro/Con" task, participants indicated their willingness to purchase fixed-price tickets for several independent gambles, each representing a poker chip being randomly drawn from a bag of exactly 100 red and blue chips. The underlying composition of the bag differed on each trial, and participants were given partial information about the amount of red chips and blue chips it contained. (The number of chips remaining unidentified was also indicated.) A red chip draw resulted in a monetary payout; a blue chip resulted in no payout. Thus the number of red chips revealed represented the amount of favorable information while the number of blue chips revealed represented the amount of unfavorable information. Both types of information were parametrically varied between 0 and 50. Behaviorally, increasing the amount of information revealed (regardless of valence) increases participants' willingness to engage in the gamble. In addition, we find an asymmetric influence of favorable over unfavorable information on willingness to purchase, replicating our prior research. Whole brain analyses reveal that activity in dlPFC, IFG, striatum, and areas in OFC significantly correlate with the amount of information (favorable+unfavorable) revealed. However, when considering the relative representation of favorable and unfavorable information, striatal activity was more strongly correlated with increasing amounts of unfavorable information. By contrast, OFC and dlPFC activity varied more according to the degree of favorable information. Collectively we find that under ambiguity, the amount of information that is available is tracked by reward-related circuitry, and there are differences in this representation for favorable and unfavorable information.

Disclosures: U.R. Karmarkar: None. **S. Ye:** None. **V. Rimeikyte:** None. **E. Kastman:** None. **J.W. Buckholtz:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.15/JJJ16

Topic: H.02. Human Cognition and Behavior

Support: NIH-NINDS 5R01NS092701
Wellcome Trust Pricipal Research Fellowhip
The Kane Family Foundation
Gatsby Charitable Foundation
Virginia Tech Carilion Research Institute
Wake Forest University

Title: Serotonin signaling in human striatum during active social exchange

Authors: *T. M. LOHRENZ[1], K. T. KISHIDA[2,3], A. HULA[4], J. P. WHITE[1], R. J. MORAN[1], A. LAXTON[2], S. B. TATTER[3], M. R. WITCHER[5], I. SAEZ[6], E. R. LAWRENCE[1], P. E. PHILLIPS[7], P. DAYAN[4], P. R. MONTAGUE[1,4,8]
[1]Virginia Tech. Carilion Res. Inst., Roanoke, VA; [2]Physiol. and Pharmacol., Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [3]Neurosurg., Wake Forest Univ., Winston-Salem, NC; [4]Wellcome Trust Ctr. for Neuroimaging, Univ. Col. London, London, United Kingdom; [5]Neurosurg., Wake Forest Sch. of Med., Winston-Salem, NC; [6]Univ. of California Berkeley, Berkeley, CA; [7]Psychiatry & Behavioral Sci., Univ. of Washington, Seattle, WA; [8]Physics, Virginia Tech., Blacksburg, VA

Abstract: Serotonin signaling is implicated in major psychiatric disorders such as depression, anxiety disorders, and anorexia. It is also thought to play a major role in decision-making in the healthy, yet its computational roles remain murky. To delineate this further, we have modified cyclic voltammetry techniques for use in human subjects undergoing electrode implantation surgery for deep brain stimulation treatment for Parkinson's disease or essential tremor (Kishida et al., 2016; Moran et al., 2018). These voltammetry measurements, taken while subjects carry out simple economic games, allow the detection of sub-second dopamine and serotonin signals related to computational variables defined by the tasks. Here we extend these results to serotonin signaling in humans engaged in active social exchange. Specifically, we examine serotonin signaling while subjects played a well-characterized multi-round trust task (N= 20; see Hula et al., 2018). We model subjects' behavior using an interactive partially observable Markov decision problem framework (iPOMDP; Hula et al., 2018) and derive a first-order inter-personal prediction error: the ongoing difference between a partner's action and what this action was expected to be. Serotonin fluctuations at the revelation of the partner's action are negative for positive first-order errors and positive for negative first order errors; thus, even in this complex, socially-defined, exchange, serotonin is apparently opponent to dopamine, which typically reports prediction errors with the opposite (i.e., normal) sign. These results suggest that the idea that serotonin is an opponent to dopamine can be extended in a principled computational way to social situations.

Disclosures: T.M. Lohrenz: None. **K.T. Kishida:** None. **A. Hula:** None. **J.P. White:** None. **R.J. Moran:** None. **A. Laxton:** None. **S.B. Tatter:** None. **M.R. Witcher:** None. **I. Saez:** None. **E.R. Lawrence:** None. **P.E. Phillips:** None. **P. Dayan:** None. **P.R. Montague:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.16/JJJ17

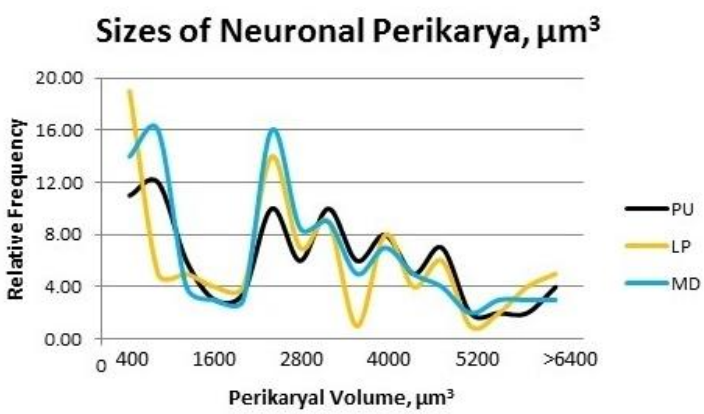
Topic: H.02. Human Cognition and Behavior

Support: BNS8204480

Title: The relative frequency of neuronal perikaryal sizes differentiates five classes in higher-order nuclei of the human thalamus

Authors: *E. ARMSTRONG, G. KAHVECI, S. LAGO, J. LENCHNER, M. ROBINSON, E. SEVER
Lake Erie Col. of Osteo. Med., Greensburg, PA

Abstract: The relative frequencies of neuronal perikaryal sizes were analyzed in different human thalamic nuclei. The data are from a normal human brain that is part of the Yakovlev Collection. Neurons were identified by their full, round nucleoli and an eye-piece micrometer measured two axes, the longest and the second at right angles to that. It is assumed that shrinkage is common throughout the thalamus and measurements were made systematically in all three dimensions of the nuclei. Although exact functional associations of soma size are not known, size is thought to reflect attributes of how information is delivered rather than of content.
Higher-order thalamic nuclei; the pulvinar (N=422), the lateral posterior nucleus (N=85), and the medial dorsal nucleus (N=242), were characterized by having a population of small neurons (400-1200 μm^3) and a larger range of intermediate sized neurons (2000-6000 μm^3). There was a scattering of a few larger perikarya in all these nuclei (>5800 μm^3). All higher-order nuclei had very few neurons in the size range (1200-2000 μm^3). The intermediate cell groups formed four distinct local maxima that overlapped each other, suggesting a concurrence of modulating properties for corticothalamic afferents. Despite their different content, each peak may form a single class. The limbic nuclei, anterior principalis (N= 70) and lateral dorsalis (N=46), resembled higher-order nuclei in having few neurons in the 1200-2000 μm^3 range, but differed, by having a single peak of intermediate sized soma.
Sensory nuclei showed a different distribution. Intermediate sized neurons in the ventroposterior lateral and medial nuclei (VPL+M; N=238) had a unimodal distribution, resembling those of motor nuclei, ventrolateral oralis (N=85) and ventrolateral caudalis and medialis (N=283), but differ in having large neurons as well. Distributions in both geniculate bodies (LGBm N=72, LGBp N=155; MGBm N=31, MGBp N=150) had local maxima and minima with little overlap, suggesting that geniculate neurons modulate according to local demands and do not form a single class.



Disclosures: E. Armstrong: None. **G. Kahveci:** None. **S. Lago:** None. **J. Lenchner:** None. **M. Robinson:** None. **E. Sever:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.17/JJJ18

Topic: H.02. Human Cognition and Behavior

Support: NRF-2015M3C7A1031969

Title: Alpha-band phase coherence modulation at right fronto-central region reflects a sustained proactive control mechanism involved in a stop-signal task

Authors: *W. LEE, E. JEONG, M.-S. KANG
Psychology, Sungkyunkwan Univ., SEOUL, Korea, Republic of

Abstract: Proactive control mechanism reflects a sustained, top-down maintenance of a goal representation in advance of task-related events while reactive control mechanism reflects a transient, bottom-up goal reactivation in response to task-related events (Braver, 2012). We designed a manual stop-signal task to isolate neural representations specifically involved in proactive control mechanism. Subjects performed a choice reaction time task but had to withhold their response to an infrequent stop-signal. We manipulated stop-signal probability (30% vs 10%) over different blocks of trials so that different proactive control levels were sustained within each block. In addition, we obtained EEG responses locked with the fixation onset to isolate neural representations of proactive control mechanisms because the fixation is uninformative to subsequent events and, thus, neural responses accompanied with the fixation onset reflect the cognitive state sustained throughout each block.

26 subjects' data (12 female, mean age 23.5) were analyzed. Reaction times (RTs) increased and erroneous responses after the stop-signal decreased with stop-signal probability, indicating that subjects changed their behavioral strategy proactively. When we analyzed the trials without stop signals in conjunction with a non-parametric permutation test and cluster-based correction, a significantly higher alpha-band inter-trial phase coherence (ITPC) modulation was identified at the right fronto-central electrode (FC6) within 400 to 800 ms after the fixation point from the 30% stop-signal block in relative to 10% block. We then conducted an inter-site phase clustering (ISPC) analysis by using the FC6 signal as a seed because previous studies have shown that frontal cognitive control mechanism impacted the target processing by modulating neural responses at the posterior and occipital areas (e.g. Zanto & Gazzaley, 2011). We found a significant theta-band ISPC modulation from occipital areas (O1 and Oz) prior to the target onset. To see whether this ISPC modulation at occipital electrodes does impact visual processing, we obtained target-locked ERPs and found a significant posterior N2 modulation between the two probability blocks. Taken together, we concluded that right fronto-central area plays an important role in adaptive behavior in advance of task-related events.

Disclosures: W. Lee: None. **E. Jeong:** None. **M. Kang:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.18/JJJ19

Topic: H.02. Human Cognition and Behavior

Support: LMU Faculty Research Grant

Title: EEG gamma activity is altered in working memory during test recall

Authors: J. G. FOY, S. M. MCQUADE, L. M. KEARNS, C. DE PIEROLA, *M. R. FOY
Dept. of Psychology, Loyola Marymount Univ., Los Angeles, CA

Abstract: An electroencephalogram (EEG) measures changes in brain electrical activity, with wireless EEG systems being particularly useful in establishing high ecological validity. In the current study, we identified EEG activity changes while participants completed a series of standardized and challenging performance-based cognitive tasks (NIH Toolbox). Wireless EEG scalp recordings (B-Alert x10 Headset, Advanced Brain Monitoring) corresponding to a wide spectrum of signal frequencies (alpha, beta, delta, gamma, sigma, theta) were recorded from 29 undergraduate participants during 1.5 hr recording sessions. Power spectral densities (PSD) were computed following artifact decontamination and data smoothing (AcqKnowledge 4.4; B-Alert Software, Biopac). Here we report the results of gamma frequency band (25-40 Hz) PSD during

an episodic working memory task (Picture Sequence Memory Test, NIH Toolbox). Gamma activity was obtained in 1 sec epochs during memory practice vs. memory task phases at 9 electrode sites (Pz, Fz, Cz, P3, P4, F3, F4, C3, C4). A repeated measures ANOVA revealed statistically significant ($p<.001$) main effects of phase and electrode site. Post-hoc tests revealed significantly increased gamma PSD during the memory task phase compared to memory practice phase at all of the electrode sites. Gamma PSD was also found to be highest at right frontal (F4) and right central (C4) electrode sites compared to all other electrode locations for both phases of the study. Our results confirm prior research that associates gamma activity with attention and memory demands. Also, our results show that increased gamma activity during the cognitive task is distributed across all electrode sites from which recordings were obtained, with highest activity recorded in right hemisphere.

Disclosures: J.G. Foy: None. **S.M. McQuade:** None. **L.M. Kearns:** None. **C. De Pierola:** None. **M.R. Foy:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.19/JJJ20

Topic: H.02. Human Cognition and Behavior

Support: NIMH (MH63901)

Title: Dissociable roles for theta and beta frequency neural oscillations in cognitive control

Authors: *D. A. VOGELSANG[1,2], J. RIDDLE[2], K. HWANG[2], D. CELLIER[2], M. D'ESPOSITO[2]
[1]Dept. of Neurosci., D'Esposito Lab., Berkeley, CA; [2]Univ. of California, Berkeley, Berkeley, CA

Abstract: Cognitive control is the ability to organize thoughts and actions according to internal goals. Mechanisms of cognitive control can be revealed by manipulating the rules subjects use to evaluate a stimulus and make an appropriate response. This type of rule learning requires flexible cognitive control, which relies on being able to execute simple concrete rules as well as more complex abstract rules. For example, a simple concrete rule is one that explicitly maps a stimulus to a response, whereas a more complex abstract rule is one where the stimulus response mapping depends on contextual factors. Cognitive control also relies on the ability to hold a number of these rules in mind simultaneously. Therefore, in addition to varying the level of abstraction, the number of rules can be increased within a single level of abstraction (set size). Previous research has found that both neuronal oscillations in theta (Voytek et al. 2015) and beta (Wutz et al. 2018)

frequencies are associated with various types of top-down cognitive control, however whether these two frequency bands play a similar or distinct roles in cognitive control remains unknown. The current EEG experiment (n=31) investigated whether the level of abstraction of a rule, and number of rules that must be maintained, are supported by neuronal oscillations in different frequency bands. Results of the time-frequency analysis in frontal electrodes showed an increase in theta power for increased set size that positively correlated with changes in reaction time, whereas a decrease in beta power was associated with increased abstraction and negatively correlated with reaction time. Our results suggest that there are distinct neural oscillatory mechanisms that underlie different aspects of top-down cognitive control. <!--EndFragment-->

Disclosures: D.A. Vogelsang: None. **J. Riddle:** None. **K. Hwang:** None. **D. Cellier:** None. **M. D'Esposito:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.20/JJJ21

Topic: H.02. Human Cognition and Behavior

Support: JSPS JP15H03062

Title: No-go specific EEG activities during response inhibition training associated specifically with subsequent chocolate eating behavior

Authors: *K. YAMANAKA
Showa Women's Univ., Tokyo, Japan

Abstract: Previous studies suggested that training to inhibit food-related responses has a potential to help modulate excessive or impulsive eating behavior. However, there are considerable inter-individual differences and food-specificity in the effectiveness of the response inhibition training. It’s partly due to a large variety of their approach to the response inhibition training and/or property of the target food. Therefore, we investigated the relationship between cortical activities during the training and subsequent food consumption of different target food. For the response inhibition training, we used a go/no-go task, in which go or no-go signal was simultaneously presented with one of the images of chocolate, manju (Japanese sweets), sio-sembei (Japanese salty snack) on the plate, or empty plate. In this study, participants were assigned to chocolate-no-go condition (n = 12) or manju-no-go condition (n = 10), in which no-go signal consistently presented with the chocolate or manju image. Before the training, an eating-related questionnaire (Dutch Eating Behavior Questionnaire: DEBQ) and subjective assessment of appetite and preference for the 3 types of foods used in this study (visual-analog

scale: VAS) were conducted. During the training, surface electroencephalogram (EEG) was recorded and traditional event-related potential (ERP) waveforms were calculated. After the training, participant was instructed to eat the 3 types of foods as she would like in a sham taste test. And finally, the number of pieces they ate was calculated for each food separately and for all 3 foods together. As a results, there was no significant difference in DEBQ score, VAS scores, and food consumption between chocolate-no-go and manju-no-go conditions. However, in both condition, manju and sio-sembei consumption positively correlate, but chocolate consumption does not correlate, with total consumption, suggesting a chocolate-specific eating behavior. Moreover, in chocolate-no-go condition, amplitude of negative ERP peak (N2) in no-go trials, which reflect response inhibition, significantly correlate with amount of chocolate intake. On the other hand, in manju-no-go condition, there was no significant correlation between amplitude of no-go N2 and manju intake. These results indicate that 1) the participants who inhibit a chocolate-related response more strongly in no-go trials eat less chocolate, and that 2) the food-related response inhibition training has an effect specific for chocolate eating behavior.

Disclosures: K. Yamanaka: None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.21/JJJ22

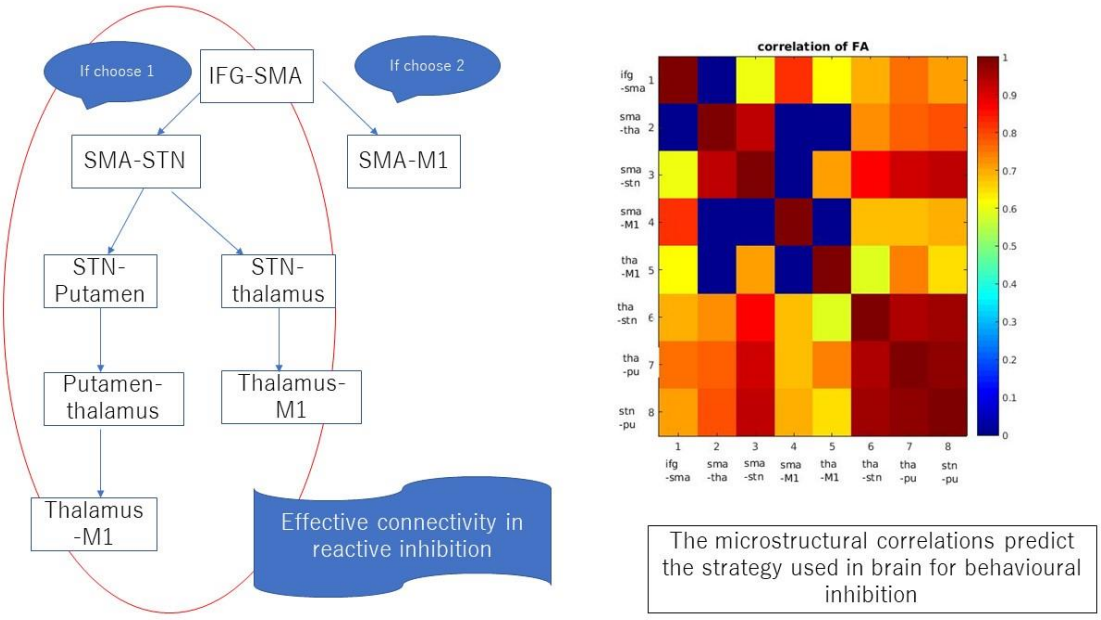
Topic: H.02. Human Cognition and Behavior

Title: The strategy in the brain: The micro-structural correlations predict the hyper-direct pathway and ‘hub’ in the reactive inhibition

Authors: *F. ZHANG[1,2], S. IWAKI[1,2]
[1]Natl. Inst. of Advanced Industrial Sci., Tsukuba, Japan; [2]Univ. of Tsukuba, Tsukuba, Japan

Abstract: A open question in the brain research is how the structural networks influence the functional interactions.The research in reactive inhibition, which triggered by the stop signal, has provided the detailed information of underlying neural system. The stop signal is received and processed by frontal cortical regions, then the command is sent to the basal ganglia to prepare or inhibit the response. Furthermore, there are increasing evidences that the hyper-direct pathway(cortico-subthalamonigral) , which is critical in quickly response inhibition by bypassing the striatum and connecting the cortex and subthalamic nucleus directly, is involved in the motion information processing. In our research, we investigated the inter-tract correlation of fractional anisotropy(FA) between cognitive control network including inferior frontal cortex(IFG), presupplementary motor area (preSMA) / supplementary motor area (SMA),

putamen, Thalamus, primary motor cortex (M1) and subthalamic nucleus, and found the involvement of hype-rdirect pathway. Furthermore, we also combined micro-structural correlation with the effective connectivity of cognitive control network, and confirmed the existence of hyper-direct pathway in both structural and functional connectivity. Meanwhile, we also proved the basal ganglia as a 'hub'in the cognitive control network. Taken together, our research provided the new perspective to investigate the influence of structure network on functional interactions, and how the function emerges from structural network in reactive inhibition.



Disclosures: F. Zhang: None. **S. Iwaki:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.22/JJJ23

Topic: H.02. Human Cognition and Behavior

Title: Neural oscillatory correlates of effort based influences on proactive inhibition

Authors: *T. TSUCHIYA[1], J. M. FINE[2], M. SANTELLO[2]
[2]SBHSE, [1]Arizona State Univ., Tempe, AZ

Abstract: Research on reinforcement-based decisions presumes that the option with the highest expected value is chosen. Furthermore, when deciding between two options with similar reward, there is typically a preference towards action with the least effort cost. There are also scenarios where one must choose between engaging (Go) in an action with some probability of reward and abstaining (No-Go) from action and without reward. Given a fixed reward, one would anticipate that increasing effort would increase inhibition over 'Go' decisions as this alone incurs a physical cost. However, the behavioral and neurophysiological indices related to effort-based choices of action engagement (Go/No-Go) remain unknown. The current study aimed to fill this gap by examining behavioral responses and EEG-based oscillatory activity while human subjects (n=13) performed a novel anticipatory stopping task. Subjects used a robotic manipulandum to perform reaching movement and hit a target location if they believed it was a Go trial. Endpoint movement occurred simultaneously with a moving bar to gain reward. In all trials, the moving bar was displayed as a specific color that was linked to the bar's probability of stopping (Pstop: 0.15, 0.4, 0.6, and 0.85) before the target. Both correct Go and No-Go responses were rewarded. In Go trials, subjects took 700 ms to reach the target. In Stop trials, the bar stopped at 475 ms. In the first block of trials, subjects' proportion of 'Go' responses matched the probability of the 'Go' cue. In the second block, we used a novel effort manipulation (3 effort levels) by implementing a velocity-dependent force field. In this effort manipulation block, we found an asymmetric effect of effort wherein the proportion of Go responses increased and decreased in trials with high and low Go probability, respectively. When comparing probability of responding in block 1 vs block 2 (with effort), higher Go probability trials (Pstop: 0.15 and 0.4) revealed larger tendencies to Go despite a higher effort in block 2, rather than decreasing these responses. This indicates that effort did not have the anticipated effect of globally decreasing Go responses, but rather increased the tendency to Go when Pstop was low and decreased it when Pstop was high. Our EEG results examined during response preparation revealed medial frontal (MF) theta power increased with Pstop (blocks 1 and 2), while MF alpha power increased by the inclusion of effort (block 2) independent of Pstop. These findings extend previous work by revealing that separate MF frequencies may represent distinct variables impinging on decision making and response inhibition.

Disclosures: T. Tsuchiya: None. **J.M. Fine:** None. **M. Santello:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.23/JJJ24

Topic: H.02. Human Cognition and Behavior

Support: FWO grant G012816

Title: EEG signature of instructed sensory-motor mapping implementation

Authors: *M. SENOUSSI, D. TALSMA, T. VERGUTS
Exptl. Psychology, Ghent Univ., Gent, Belgium

Abstract: Humans can create arbitrary associations between stimuli and actions (sensory-motor mappings). These mappings allow us to flexibly implement complex behavior depending on context or instructions. On short time scales these mappings cannot be subtended by structural changes in neural networks, but must instead be created through functional networks built on the fly. In this study we investigated the electrophysiological signature of preparing sensory-motor mappings instructed on a trial-by-trial basis. We recorded EEG with 64 electrodes while participants prepared instructed sensory-motor mappings to perform a 2-Alternative Forced Choice orientation discrimination task on one of two gratings using either their left or right hand (depending on the instruction). Each trial started with instructions in the form of two letters, one above and one below the fixation cross. These letters were either 'L' (for Left) or 'R' (for Right) and instructed participants which grating was the target (letter above the fixation cross), and which hand to use to report the tilt direction (letter below the fixation cross). Instructions were followed by a variable-duration interval (1700-2200ms) to prepare the instructed mapping. Then two gratings were presented, one on each side of the fixation cross. Tilt level was titrated to reach ~75% accuracy for each participant before the experiment. To uncover neural activity selective to the preparation of the different sensory-motor mappings we used a Linear Discriminant Analysis classifier based on spatial patterns of EEG activity. As inputs to the classifier we used either scalp potentials (for each time point and electrode) or spectral amplitude (for each time point, oscillatory frequency, and electrode). Using scalp potentials we were able to classify the mapping during the preparation interval. Classification accuracy reached 45% (chance level 25%) and was sustained above chance level between 170ms to 950ms. Classification on spectral amplitudes revealed selective classification accuracy up to 52% between 600ms and 1500ms in alpha (8-12hz) and beta (13-30hz) frequencies. This demonstrates that sensory-motor mapping information is present in the EEG signal extremely rapidly and before stimulus onset.

Disclosures: M. Senoussi: None. **D. Talsma:** None. **T. Verguts:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.24/JJJ25

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS-1455866

Title: Transcranial focused ultrasound over right inferior frontal gyrus improves response inhibition

Authors: *M. SANTELLO, J. M. FINE, M. FINI, W. J. TYLER
Sch. of Biol. and Hlth. Systems Engin., Arizona State Univ., Tempe, AZ

Abstract: Inhibitory control over impending or ongoing actions is essential for success in activities of daily living. Response inhibition has been studied extensively using the 'stop signal task' (SST) where subjects cancel actions in response to an infrequent stop cue. Correlational studies (EEG, fMRI), lesion studies, and neuromodulation studies (TMS) have identified a reactive stopping network involving pre-SMA, subthalamic nucleus, and *pars opercularis* in the right inferior frontal gyrus (rIFG), with rIFG being the area most repeatedly linked to inhibition. With regard to neuromodulation studies, offline TMS protocols have provided mixed results by revealing increased or decreased stopping performance dependent on the stimulation protocol. One issue with TMS is that it can potentially elicit neural activity in several neighboring areas. Because these TMS investigations are applied offline and induce large artifacts in electrophysiological measures of cortical activity (e.g., EEG), online neural measures and TMS have not been paired. Thus, it is unclear how rIFG TMS effects on inhibition translates into neural processes implicated with response inhibition, and therefore evidence from human studies remains correlative. Here we examined the role of rIFG during a SST (35% stop trials) using MRI stereotaxically-guided 0.5 MHz transcranial focused ultrasound stimulation (tFUS). tFUS has several advantages over all other non-invasive stimulation methods, including (1) the beam is precise within a 5-mm^2 region, allowing us to specifically target *pars opercularis*, and (2) there are no current spread or artifacts, allowing us to simultaneously stimulate and measure EEG. We used 4 levels of stop-signal delay determined as percentages of baseline of 'Go' reaction time distribution from all trials. During tFUS trial, the stimulation trains lasted 300 ms and were applied at either visual Go or Stop signal onset. tFUS improved the proportion of correctly inhibited responses (18% improvement), but only when tFUS was applied coincident with the Stop signal. Importantly, this effect of tFUS was not found in a control group (tFUS over ipsilateral S1). EEG analysis of rIFG group data revealed tFUS increased theta and beta activity measured over preSMA and rIFG. Surprisingly, tFUS increased directed-phase connectivity from preSMA to rIFG, but not vice versa. These results provide strong support for the role of *pars opercularis* in reactive inhibition, and provide the first demonstration that tFUS can be used online to identify key neural nodes for cognitive and executive functions in humans.

Disclosures: M. Santello: None. **J.M. Fine:** None. **M. Fini:** None. **W.J. Tyler:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.25/JJJ26

Topic: H.02. Human Cognition and Behavior

Support: NIH R01 NS102201

Title: Electrophysiological evidence for common processing of task-switching and novelty processing

Authors: *T. R. DYKSTRA, E. HAZELTINE, J. R. WESSEL
Univ. of Iowa, Iowa City, IA

Abstract: Orienting attention to salient events and using feedback to adapt ongoing behavior are critical components of cognitive flexibility. Research suggests that cued task-switching and processing infrequent events may rely on a common cognitive system, indexed by a frontocentral P3 wave (Barcelo et al., 2006). Here we investigate the relationship between novelty detection and *feedback-driven* switching by measuring frontocentral P3 amplitude in three paradigms requiring varying degrees of task-switching and novelty detection. In this way, we also test a possible shared network for stimulus-driven (e.g., novelty) and feedback-driven (e.g., switching) behavioral adaptation.

Participants completed a feedback-driven task-switching paradigm in which switches occurred by changing response mappings rather than changing the relevant stimulus dimension. Subjects also completed a separate task containing irrelevant infrequent stimuli but no switches. Finally, participants performed a combined infrequency/switch task where comparing feedback to response determined the correct response mapping for the next trial, but irrelevant infrequent events were also present.

We applied ICA to the novelty task portion of the EEG dataset to identify a frontocentral P3 component, which showed increased activity on novel vs. standard trials. We then investigated the activity of this component in the task-switching tasks and observed increased activity on switch vs. repeat trials. We observed the same pattern of results when repeating the analysis and identifying a frontocentral P3 component from the task-switching portion of the EEG dataset and comparing to the novelty tasks.

Our results imply that behavioral adaptations during task-switching and novelty detection may be implemented via a common neural network. Theoretical accounts propose that this network may involve the subcortical subthalamic nucleus (STN; Wessel & Aron, 2017). Therefore, we collected intracranial recordings from Parkinson's patients undergoing implantation of deep brain stimulators in the subthalamic nucleus during the task-switching task. Preliminary results

show sustained increases in STN β-power for switch as compared to repeat trials, confirming a potential involvement of the STN.
We extend previous work on task-switching to show that the link between novelty and switching based on stimulus dimension also applies to switching with respect to response mappings. Moreover, our results suggest a common network for stimulus- and feedback-driven behavioral adaptation, as suggested by prior work. Lastly, our results provide first evidence for the subcortical STN in task-switching.

Disclosures: T.R. Dykstra: None. **E. Hazeltine:** None. **J.R. Wessel:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.26/JJJ27

Topic: H.02. Human Cognition and Behavior

Support: NIH DA 026452

Title: Successfully stopping a movement has global motor effects as evident in a pause of tonic EMG of a task-unrelated effector

Authors: *S. JANA, A. R. ARON
Dept. of Psychology, Univ. of California San Diego, San Diego, CA

Abstract: Rapid stopping of action is an everyday requirement. In the lab, it is often studied using the Stop Signal or Go/NoGo tasks. Rapid action stopping appears to have global motor effects as demonstrated by several studies that have measured corticospinal excitability with Transcranial Magnetic Stimulation (TMS). When one effector is stopped (such as voice or eyes) there is decreased corticospinal activity for a task-unrelated effector (such as hand or leg) (Badry et al. 2009; Cai et al. 2012; Majid et al. 2012; Wessel et al. 2013). This global motor effect correlates with signals recorded from the subthalamic nucleus (Wessel et al. 2016), and may reflect the operation of a prefrontal-subthalamic nucleus 'hyperdirect' pathway (Nambu et al. 2002) which has a broad suppressive effect on the basal ganglia output. Yet further investigations of this global suppression are hampered by the method of using TMS to measure corticospinal excitability. Not only is this inconvenient for many labs, but it also requires an exorbitant number of trials to map the temporal profile.
Here we tested a novel approach of studying the temporal profile of global motor suppression by measuring electromyography activity (EMG) in a task-unrelated muscle. We asked subjects to perform the Stop Signal task with their right hand while they continuously pressed a squeeze ball between their left hand thumb and forefinger. We measured EMG activity from the first dorsal

interosseous muscle of the left hand using surface electrodes. In accordance with the findings from TMS, and in two separate experiments (each N = 20), we observed a decrease in the task-unrelated tonic EMG activity for Correct Stop trials compared to both Correct Go and Failed Stop trials. This decrease was quite rapid (~80 after the Stop Signal) and transitory, lasting until about the Stop Signal Reaction Time, a metric of the time taken to stop a movement. Further research will investigate the effectiveness of this method in elucidating global suppression in error and conflict scenarios.
Global motor suppression is a proxy for a fast stopping process, and possibly a proxy for a hyperdirect frontal-subthalamic circuit with a global impact on basal ganglia output. This EMG approach provides a novel method for easily testing whether and when global motor suppression occurs in different task contexts.

Disclosures: S. Jana: None. **A.R. Aron:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.27/JJJ28

Topic: H.02. Human Cognition and Behavior

Support: KAKENHI Grant 16H06405
KAKENHI Grant 15J0082

Title: Hypoxic exercise-induced cognitive fatigue depends on arterial oxygen desaturation: A neuroimaging study

Authors: *G. OCHI[1,2], H. SOYA[1,2]
[1]Lab. of Exerc Biochem & Neurosci, Univ. of Tsukuba, Tsukuba-Shi, Japan; [2]Dept. of Sports Neuroscience, Advanced Res. Initiative for Human High Performance, Univ. of Tsukuba, Tsukuba-Shi, Japan

Abstract: Exercise-induced fatigue consists of central fatigue, such as reduction of central motor command, and the peripheral fatigue in muscle. This exercise-induced central fatigue may also deteriorate executive function mediated by prefrontal cortex (cognitive fatigue) and worse athletic performance. We found that 10 min moderate exercise under moderate hypoxic condition (FIO_2 = 0.13) lowers dorsolateral prefrontal cortex (DLPFC) activity and decrease executive function (Ochi et al., *NeuroImage*, 2018). Although mechanisms behind cognitive fatigue are still unclear, cerebral hypoxia caused by decreasing arterial oxygen saturation (SpO_2) is thought as one of the important factor of exercise-induced cognitive fatigue. Thus, the purpose of this study was to clarify the effect of arterial desaturation during hypoxic exercise on

cognitive fatigue by using our special hypoxic exercise model and to clarify the underlying neural mechanisms by using multichannel functional near-infrared spectroscopy (fNIRS). Fourteen healthy subjects underwent moderate intensity exercise (50%VO_{2peak}) under two conditions: moderate (FIO_2 = 0.13)(MOH) or mild hypoxic conditions (FIO_2 = 0.16)(MIH). All subjects performed color-word Stroop task (CWST) before and after exercise under moderate hypoxic condition (FIO_2 = 0.13). Cognitive performance was assessed by reaction time (RT) of CWST. The difference in RT between incongruent and neutral trial of CWST was calculated as $RT_{interference}$ to determine executive function. fNIRS probes were put over the forehead during the CWST and we monitored brain activity in left sides of the DLPFC what plays a crucial role in executive function. Task-related oxy-Hb concentration change was used as an indication of brain activity. Arterial oxygen saturation (SpO_2) were monitored during experiment. As the results, SpO2 significantly decreased during exercise in MOH compared with MIH (MIH: 88.4±1.7%; MOH: 79.5±3.6%). On the other hand, there was not significant difference on SpO_2 during CWST between both conditions (MIH: 89.2±2.0%; MOH: 88.6±1.6%). Regarding $RT_{interference}$ and brain activity, two-way ANOVA showed significant interactions between time (pre/post) and condition (MOH/MIH). Post-hoc analyze revealed that delayed $RT_{interference}$ and decreased task-related oxy-Hb concentration change in left DLPFC in MOH compared with MIH. These results indicate that negative effect of hypoxic exercise on executive function was cancelled by suppressing SpO_2 reduction during hypoxic exercise. Hypoxic exercise-induced arterial desaturation lowers task-related prefrontal activity and deteriorate executive function.

Disclosures: G. Ochi: None. **H. Soya:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.28/JJJ29

Topic: H.02. Human Cognition and Behavior

Support: NIH NIDA DA 026452

Title: Preparing to stop and preparing to go have dissociable signatures in sensorimotor beta and mu

Authors: *V. MURALIDHARAN[1], X. YU[1], M. X. COHEN[2], A. R. ARON[1]
[1]Dept. of Psychology, Univ. of California San Diego, La Jolla, CA; [2]Radboud Univ., Nijmegen, Netherlands

Abstract: We are interested in how people proactively set their motor system into a suppressed state so that they can stop better in the future. Here we used scalp EEG to test the hypothesis that

this proactive suppressive state might correspond to increased beta band power. Human subjects performed a task which required them prepare to stop an action in the future. On each trial, a cue instructed them to prepare to stop the left or right hand, or to prepare to move the left or right hand. After a delay of 1000 ms they had to make a bimanual movement, and, on a minority of trials to try to stop the earlier cued hand while continuing with the other. We analyzed scalp EEG data in 16 subjects using Generalized Eigenvalue Decomposition (GED). This looks for a subspace of weights which optimally separates signals from two conditions (here, the 1000 ms cue period where they prepared to stop the left or right hand). In all subjects, we found components with a contralateral sensorimotor topography in the beta frequency (12-20 Hz). Importantly, power in this component correlated trial-by-trial with the ability to selective suppress when required (Prepare to Stop Right: $r = -0.13$, $p<0.05$; Prepare to Stop Left: $r = -0.15$, $p<0.05$). Interestingly, doing a similar analysis in the cue period for preparing to move a hand (as opposed to preparing to stop) now revealed sensorimotor components at a lower frequency (mu) (Average preparing to Go: 10.40 Hz; Average preparing to Stop: 15.03 Hz). We thus show that preparing to stop a particular hand has an EEG signature of increased beta band power in contralateral sensorimotor regions. The degree of power in this component relates to the ability to subsequently selectively stop a response. Moreover, this suppressive state has a different signature from preparing to go. These findings raise interesting questions about the physiology of sensorimotor circuits for stopping and going, prove the utility of the GED method as an effective spatial filter for response control, and pave the way for real-time feedback approaches.

Disclosures: V. Muralidharan: None. **X. Yu:** None. **M.X. Cohen:** None. **A.R. Aron:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.29/JJJ30

Topic: H.02. Human Cognition and Behavior

Support: NIH NIDA DA026452

Title: Preventing a thought from coming to mind elicits increased right frontal beta just as stopping action does

Authors: *A. CASTIGLIONE[1], J. WAGNER[2], M. C. ANDERSON[3], A. R. ARON[4]
[1]LA Jolla, CA; [2]Dept. of Psychology, Univ. of California San Diego, La Jolla, CA; [3]Med. Res. Council, Univ. of Cambridge, Cambridge, United Kingdom; [4]UC San Diego, La Jolla, CA

Abstract: How do we stop thoughts and memories from coming to mind? It is possible that preventing retrieval recruits a similar stopping mechanism as motor stopping. Rapidly stopping

action requires the integrity of the right inferior frontal cortex, for which, for the stop signal task, a specific electrophysiological signature is increased beta band power for successful vs. failed stop trials, before stop signal reaction time. Here we tested whether the same signature would be elicited by the requirement to prevent an unwanted thought from coming to mind.
We recorded scalp EEG during a Think/No-Think behavioral paradigm and a subsequent stop signal task, in each of 42 participants. In the first phase of Think/No-Think participants learned word pairs. In a second phase, they were presented the left-hand word as a cue, and asked to either think about (Think trial) or not to think about (No-Think trial) the target right-hand word. At the end of each trial, they were also asked whether they had experienced an intrusion. In a final phase, they were given the cue and asked to recall the target word.
Behaviorally, we reproduced the standard finding of worse final recall for items always presented in No-Think trials, and of decreased intrusions with increasing practice for No-Think trials. For EEG, we reproduced the finding that rapid action stopping elicited increased right frontal beta power, greater for successful vs. failed stop trials, before stop signal reaction time. Critically, we observed that No-Think vs. Think trials also elicited increased right frontal beta power, within about 200ms of the No-Think cue, and this was also greater for No-Think trials where there was not a reported intrusion.
Our findings show that the requirement to prevent a thought from coming to mind quickly recruits a similar EEG signature as stopping action. This is consistent with the theory that a prefrontal stopping system also affects long term memory retrieval.

Disclosures: A. Castiglione: None. **J. Wagner:** None. **M.C. Anderson:** None. **A.R. Aron:** None.

Poster

697. Human Cognition and Behavior: Decision Making and Reasoning: Physiology and Basic Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 697.30/JJJ31

Topic: H.02. Human Cognition and Behavior

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, A2295R, B6453R)
NIDCD (R01DC009899)
NIDCD (R01DC014034)
MGH-Deane Institute
The Executive Committee on Research (ECOR) of Massachusetts General Hospital
ALS Association Milton Safenowitz Postdoctoral Fellowship
Larry and Pamela Garlick Foundation

Title: Decision related signals at single-neuron resolution in human motor cortex

Authors: *S. N. FLESHER[1,2], C. CHANDRASEKARAN[2], F. R. WILLETT[1,2], S. D. STAVISKY[1,2], M. WANG[3], P. G. REZAII[1], L. R. HOCHBERG[8,9,11,12,10], J. M. HENDERSON[1], K. V. SHENOY[2,4,5,6,7]
[1]Dept. of Neurosurg., [2]Electrical Engin., [3]Neurosciences Program, [4]Bioengineering, [5]Neurobio., [6]Howard Hughes Med. Inst., [7]Bio-X Program, Stanford Univ., Stanford, CA; [8]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VA Med. Ctr., Providence, RI; [9]Sch. of Engin., [10]Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [11]Neurol., Massachusetts Gen. Hosp., Boston, MA; [12]Neurol., Harvard Med. Sch., Boston, MA

Abstract: Considerable work recording intracortically in animal models and non-invasively in human participants has demonstrated the involvement of sensorimotor brain areas in decision making. This activity has not yet been observed in human motor cortex at single-neuron resolution. In a brain-computer interface (BCI), in which a user's motor intention is estimated, the presence of cognitive signals in a region that is being used for motor control could pose problems for accurately estimating user intention. Here, we sought to identify activity related to decision making during movement in human motor cortex with single-unit resolution.
We recorded from intracortical electrode arrays chronically implanted in the hand region of a BrainGate2 pilot clinical trial participant's (T5) motor cortex during a perceptual decision making task (Chandrasekaran et al. Nat Comm 2017). The participant observed a red and green colored grid and determined if the grid contained more red or green squares. The participant reported his decision as soon as he decided, with either an overt head movement to the target of the corresponding color, or by moving a BCI-controlled cursor to the target.
The color coherence of the grid ranged from 0.44% to 80%, and the participant's unsigned coherence threshold was found to be less than 10%, which is consistent with previously established NHP and human thresholds on the task. The recorded neurons exhibited decision-related activity in the form of sustained activity before movement onset that was separable by intended target, task coherence (difficulty) and reaction time. This sustained, pre-movement activity that encodes stimulus characteristics provides the first evidence with single-neuron resolution for decision-related activity in human motor cortex.
The presence of decision-related signals in human motor cortex both enables the opportunity to study single-neuron population dynamics in sophisticated decision tasks and highlights the necessity of taking these signals into account. More specifically, decision-related signals could otherwise appear as uncontrolled neural variability, potentially interfering with BCI control in settings with multiple potential goals. Furthermore, once identified as such, decision-related signals could be used to augment BCI control.

Disclosures: S.N. Flesher: None. **C. Chandrasekaran:** None. **F.R. Willett:** None. **S.D. Stavisky:** None. **M. Wang:** None. **P.G. Rezaii:** None. **L.R. Hochberg:** None. **J.M. Henderson:** F. Consulting Fees (e.g., advisory boards); serves on Medical / Scientific Advisory Boards of Circuit Therapeutics, Enspire DBS, and Neuropace. These entities did not support this work. **K.V. Shenoy:** F. Consulting Fees (e.g., advisory boards); consultant to Neuralink Corp.

and on the Scientific Advisory Boards of CTRL-Labs Inc., MIND-X Inc., Inscopix Inc. and Heal Inc. These entities did not support this work..

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.01/JJJ32

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH NIA AG037868
NIH NIA AG 057461
NIH UL1 TR001998

Title: Declining RNA integrity is associated with selectively weakened detection of mitochondrial pathway genes in human cadaver brain tissue samples

Authors: *E. S. JOHNSON, K. HARGIS-STAGGS, E. M. BLALOCK
Dept. of Pharmacol. and Nutritional Sci., Univ. of Kentucky, Lexington, KY

Abstract: RNA degradation can be influenced by many factors, including *post-mortem* interval and tissue pH. The degree to which RNA is degraded prior to quantification affects downstream measurement (e.g., *in situ* hybridization, RT-PCR, transcriptional profiling). Agilent Technologies introduced the RNA Integrity Number (RIN) in 2006, and over the last decade RIN has become widely adopted as a *de facto* standard to quantify RNA degradation across samples and labs. Recent studies have shown that RIN (ranging from 1- worst, to 10- best) influences mRNA levels, though relatively little work has been done to determine whether that RNA damage is random or is targeted to certain biological pathways. We hypothesized that RIN's influence on gene expression would:
a) show a strong positive correlation in control tissue (degrading RNA signal as RIN declines)
b) show a robust effect across independent studies
c) target mRNA in specific pathways
To test this, we identified and downloaded four publically available human post-mortem transcriptional profiling datasets that included disambiguated RIN scores for each array, used Affymetrix transcriptional profiling technology, and examined *post-mortem* human frontal cortex samples. To isolate RIN-selective effects, only the profiles of control samples from within each study were examined. RIN was tested for correlation with each gene's relative expression level within each study. In general, RIN correlations to gene expression in individual studies showed False Discovery Rates in the 0.15-0.3 range, indicating a relatively strong 'RIN Effect'. To determine whether this RIN Effect was robust across studies, the two studies with the strongest RIN Effects were statistically analyzed for similarity. We report a consistent and selective correlation between worsened RIN and declining mitochondrial gene expression, suggesting that

pockets of subcellular RNA close to mitochondria may be more adversely affected during the course of RNA degradation in human brain tissue. Our results further indicate that this RIN-gene expression correlation becomes pronounced when RIN < 7.5. Finally, these results indicate that this RIN Effect may create transcriptional pathway-specific blind spots that are not amenable to downstream RIN-correcting strategies.

Disclosures: E.S. Johnson: None. **K. Hargis-Staggs:** None. **E.M. Blalock:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.02/JJJ33

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH F30 MH115584

Title: Machine learning for genome based diagnosis and mechanism discovery in autism spectrum disorder

Authors: *D. N. AMATYA[1], S. T. SCHAFER[1], G. MCVICKER[2], T. O. SHARPEE[3], S. NAVLAKHA[5], F. H. GAGE[4]
[1]Lab. of Genet., [2]Integrative Biol. Lab., [3]CNL-T, [4]LOG-G, Salk Inst., La Jolla, CA; [5]The Salk Inst., La Jolla, CA

Abstract: Background:
Autism Spectrum Disorder (ASD), is a heritable neurodevelopmental condition that is defined by social, behavioral, and cognitive deficits. Affecting 1 in 68 children in the US, it is among the most devastating disorders of childhood in terms of prevalence, morbidity, and impact on society. An open problem in ASD is the lack of clinical grade biomarkers that can aid in diagnosis, as well as an incomplete understanding of disease mechanisms at the molecular level. Standard genome-wide association studies have struggled to solve this problem, because of the limited effect size of individual variants. Instead, we propose to use machine learning algorithms that are capable of considering the combinatorial effects of numerous genes simultaneously.
Methods:
In this work, we describe the application of machine learning to the genetic and clinical data contained in the Autism Speaks MSSNG database, currently the largest repository of ASD genomic data. Specifically, 1) we construct a novel representation of an individual genome as a vector of mutation burden across all genes, 2) detail the construction of classifiers (e.g. logistic regressor, random forest, support vector machines, artificial neural network) that are capable of inputting these genomic vectors and outputting the likelihood of ASD diagnosis, and 3) apply methods for “reverse engineering” these classifiers to identify individual and population ASD

risk genes.
Results:
Genomic data were acquired for 7,500 control and ASD subjects. Variant calls were parsed and scored to create genomic vectors for each subject, resulting in an efficient and informative data representation for machine learning. Using standard training and cross-validation techniques, a variety of classifiers were trained to identify ASD genomes with high accuracy (greater than 90%). In comparison to linear classification methods, such as Naive Bayes, these methods demonstrated superior performance. Finally, examination of salient genes used by the classifiers revealed overlap with known ASD genes, as well as novel potential ASD genes.
Conclusions:
Modern machine learning methods, which are capable of learning complex nonlinear functions, are able to identify patterns of mutation with diagnostic relevance in ASD. The potential impact of this work is significant, as pre-symptomatic diagnosis could facilitate the preventative management of ASD, thereby affording patients the best chance for normal development. Additionally, the discovery of new ASD related gene patterns could inform novel biological experimentation to trace disease mechanisms and therapeutic targets.

Disclosures: D.N. Amatya: None. **S.T. Schafer:** None. **G. McVicker:** None. **T.O. Sharpee:** None. **S. Navlakha:** None. **F.H. Gage:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.03/JJJ34

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant R01MH104261
ONR Grant N00014-12-1-0366
NIDA Grant U01DA043098
Hope for Depression Research Foundation

Title: Exploring differences in hippocampal gene expression across three different animal models of mood disorder: Prototyping a meta-analysis pipeline

Authors: *H. KHALIL[1], M. H. HAGENAUER[2], C. AYDIN[3], Q. WEI[4], F. MENG[1], B. S. MCEWEN[5], C. NASCA[6], S. J. WATSON, Jr.[2], H. AKIL[2]
[1]The Univ. of Michigan, Ann Arbor, MI; [2]Univ. of Michigan, Ann Arbor, MI; [3]molecular and behavioral neuroscience institute, Universty of Michigan, Ann Arbor, MI; [4]Mol. & Behav. Neurosci. Inst., Univ. of Mich., Ann Arbor, MI; [5]Lab. of Neuroendocrinology, Rockefeller Univ., New York, NY; [6]Neuroendocrinology, The Rockefeller Univ., New York, NY

Abstract: The Hope for Depression Research Foundation (HDRF) focuses on the neurobiology of mood disorders and brings together five research groups which have been using transcriptomic studies to gain insight intoanimal models of depression.Since each animal model typically represents one dimension of the plethora of changes that might be occurring within the brains of depressed individuals, integrating the results from across these studies is essential for gaining a better understanding of the biology of mood disorders. However, analyzing the results of experiments across all these studies is statistically challenging given the different species, platforms, technologies, experimental designs and statistical methodologies used. Here we developed an analysis pipeline and meta-analysis technique in order to extract consistent gene expression signatures across animal models and platforms. We tested this pipeline using five data sets from three animal models: selectively-bred high responder (HR) and low responder (LR) rats, Flinderssensitive and resistant rats, and mice with glucocorticoid receptor overexpression (early life and lifetime). The whole hippocampus or dentate gyrus was analyzed in these studies using either microarray or RNA-Seq. In order to ensure comparability, the raw data from each study was first run through our proposed pipeline for annotation, quality control, and data preprocessing. We calculated the effect size (Hedge's *g*) for each gene from each study from the moderated t-statistic obtained as the result of a differential expression analysis conducted within the limma or limma-voom pipeline. This effect size was then used within a multi-level, random effects meta-analysis model which allows grouping of the experiments by biologically relevant variables, such as species. Interestingly, we find that preliminary results point to several hundred candidate genes which show similar differential expression in the hippocampus across these animal models of mood disorder despite the fact that a superficial comparison indicated minimal intersection between the top results from each individual study. These differentially expressed genes are enriched within particular biological pathways: down-regulated genes are enriched within pathways related to synaptic function, and upregulated genes are enriched within pathways related to cell adhesion, vascular development, extracellular matrix, methylation, and inflammation. We conclude that it is beneficial to integrate results from various different models in order to understand the neurobiology of mood disorder.

Disclosures: H. Khalil: None. **M.H. Hagenauer:** None. **C. Aydin:** None. **Q. Wei:** None. **F. Meng:** None. **B.S. McEwen:** None. **C. Nasca:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.04/JJJ35

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant UM11HG006370

Title: A meta-analysis of multimodal gene co-expression networks in several regions of the mammalian brain as a basis for predicting novel neurobehavioral gene-phenotype associations via semi-supervised statistical machine learning

Authors: J. WILLIAMS[1], *P. M. NOLAN[1], M. SIMON[1], A.-M. MALLON[1], G. GKOUTOS[2]
[1]MRC Harwell Inst., Harwell Campus, United Kingdom; [2]Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Several neurobehavioral disorders are often marked by genetic heterogeneity, suggesting networks of genes contributing to symptoms presented by patients. This is especially true in autism and heritable ataxias; both conditions are associated with disparate phenotypes and gene markers in many brain regions. In this work we built multiple networks from gene expression studies in mouse and performed network meta-analyses to characterize brain network changes in 20 brain regions. We captured correlated genes in regions from thousands of publicly available RNA-Sequencing studies to provide robust evidence of weighted gene co-expression networks in mammalian brain tissues. Within each region of interest, we also created gene co-expression networks from RNA in-situ hybridization from the Allen Brain Atlas to correlate genes' spatial expression. Hierarchical clustering based on dissimilarity and topology were used to create densely connected modules within each brain-region and experimentally based network. Permutation tests were used to ensure the statistical stability of modules. Valid modules were functionally characterized by pathway enrichment analyses, multiple species phenotype enrichment and the semantic similarity of module genes' ontological annotations. Several modules were enriched with neurobehavioral phenotypes presented by humans diagnosed with spinocerebellar ataxias and on the autism spectrum. To further prioritize novel genes within these communities, these phenotypes were individually diffused throughout modules onto neighboring genes via random walks with restart in diffusion kernels. This enabled us to rank genes by their degree of co-expression, a guilt-by-association approach, with other genes in modules already enriched with patient relevant phenotypes. To validate our predicted genes associated with autism phenotypes, we have obtained patient data from the Simmons Foundation for Autism Research Initiative. Using the Neuro Behavioral Ontology, we have annotated patients' clinical outcomes to phenotypes discovered in the cohort. Future work is performing genome association studies for each phenotype encoded as above, and we will use these data as validation of our prioritized gene/phenotype associations relevant for autism. Ultimately, this study will present communities of genes associated with brain region-specific behavioral traits, and provide a ranking of both known and predicted genes which contribute to said traits. Using phenotype ontologies as our predictive ground truth will facilitate confirmation of predicted gene/trait associations by in-vivo experimentation in mouse.

Disclosures: J. Williams: None. **P.M. Nolan:** None. **M. Simon:** None. **A. Mallon:** None. **G. Gkoutos:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.05/JJJ36

Topic: I.02. Systems Biology and Bioinformatics

Support: Sloan Research Fellowship, the Whitehall Foundation (2017-12-73)
National Science Foundation (1736028)

Title: Deconvolvution of bulk rna sequencing data to estimate neuron type abundance across human cortical regions

Authors: *R. J. LOUGHNAN, T. DONOGHUE, B. VOYTEK, E. A. MUKAMEL
Cognitive Sci., Univ. of California San Diego, La Jolla, CA

Abstract: Single cell RNA sequencing (scRNA-Seq) is a valuable tool for classifying cell types based on gene expression. However, current scRNA-Seq datasets from the human brain are limited to a sparse subset of cortical regions. By contrast, RNA-Seq data from samples of whole brain tissue, also called bulk RNA-Seq, has been generated across many human brain regions and multiple developmental time points. Differences in gene expression across human brain regions have been related to spatial variability in physiological measures from functional brain imaging data, and to regional differences cortical architecture. These data suggest specific genes that are implicated in functional differences throughout the brain, but they do not give insight as to the neuron cell types driving these differences. By creating a human neuron cell type atlas with high spatial sampling, we could enable a molecular interpretation of cell types driving topological differences found in structural and functional brain imaging. Here, we present a method for estimating cell type proportions at over 100 locations across the human brain by combining single-cell RNA-Seq data with spatially resolved bulk transcriptomes.
Our method uses single cell and single nucleus RNA-Seq data from human cortex to create prototype gene expression profiles for cell types, including glial cells and excitatory and inhibitory neuronal sub-types. Graph-based Louvain clustering was used to define cell types. We integrated these single cell data with bulk RNA-seq from 120 locations sampled in 2 post mortem male human brain donors (ages 24 and 39 years; Allen Institute for Brain Science, 2013). By fitting a generalized linear regression model with non-negative coefficients for each cell type, we are able to deconvolve the bulk RNA-Seq data and estimate the proportion of each cell prototype contributing to the bulk sample.
The estimates of cell type proportions are stable and reproducible within technical replicates of the same cortical brain region within a donor. We validated our deconvolution results by repeating the analysis using independent subsets of genes. Deconvolution of bulk RNA-Seq data using prototype transcriptomes from single-cell RNA-Seq data is a promising approach to

estimate cell type proportions across brain regions. This technique could be applied in situations where single-cell RNA-Seq may be challenging, such as analysis of frozen or archived brain samples.

Disclosures: R.J. Loughnan: None. **T. Donoghue:** None. **B. Voytek:** None. **E.A. Mukamel:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.06/JJJ37

Topic: I.02. Systems Biology and Bioinformatics

Support: UCSF Program for Breakthrough Biomedical Research
NIMH R01MH113896
UCSF MSTP

Title: Variation among intact tissue samples reveals the core transcriptional features of human CNS cell classes

Authors: *K. W. KELLEY[1], H. NAKAO-INOUE[2], A. V. MOLOFSKY[2], M. C. OLDHAM[3]
[2]Psychiatry, [3]Neurolog. Surgery, [1]Univ. of California San Francisco, San Francisco, CA

Abstract: It is widely assumed that cells must be physically isolated to study their molecular profiles. However, intact tissue samples naturally exhibit variation in cellular composition, which drives covariation of cell-class-specific molecular features. By analyzing transcriptional covariation in 7221 intact CNS samples from 840 individuals representing billions of cells, we reveal the core transcriptional identities of major CNS cell classes in humans. By modeling intact CNS transcriptomes as a function of variation in cellular composition, we identify cell-class-specific transcriptional differences in Alzheimer's disease, among brain regions, and between species. Among these, we show that *PMP2* is expressed by human but not mouse astrocytes and significantly increases mouse astrocyte size upon ectopic expression *in vivo*, causing them to more closely resemble their human counterparts. Our work is available as an online resource (http://oldhamlab.ctec.ucsf.edu) and provides a generalizable strategy for determining the core molecular features of cellular identity in intact biological systems.

Disclosures: K.W. Kelley: None. **H. Nakao-Inoue:** None. **A.V. Molofsky:** None. **M.C. Oldham:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.07/JJJ38

Topic: I.02. Systems Biology and Bioinformatics

Title: Translating ribosome affinity purification (TRAP) molecular profiling of CNS cell types: A data resource for the neuroscience community

Authors: *J. P. DOYLE[1,2], J. A. VEKICH[1], K. BOBKOV[1], C. S. HOLUB[1], D. DAS[1], R. YAMASHITA[1], M. EKSTRAND[1], A. AMADOR[1], E. BOSHOFF[1], P. TASKAR[1], H. SCHIFFER[1,2], J. ATIENZA[1], J. SERRATS[1], N. CHEN[1], E. YOO[1], G. CORBETT[3], J. POWELL[3], N. BRICE[3], N. KAUSHAL[1,2], W. J. RAY[1,2]
[1]Takeda California, San Diego, CA; [2]Envoy Therapeut., Jupiter, FL; [3]Takeda Cambridge, Cambridge, United Kingdom

Abstract: The Translating Ribosome Affinity Purification (TRAP) methodology was developed in the labs of Nathaniel Heintz and Paul Greengard at Rockefeller University in order to overcome the inherent complexity of brain tissues and to obtain cell-type specific translational profiles of critically relevant neural cell types (Doyle et al., Heimann et al., Cell, 2008). Using bacTRAP transgenic mouse lines licensed from Rockefeller University or generated in-house, we have collected a large amount of both microarray and RNAseq TRAP data for numerous neural cell types, both in a basal state as well as in animal models relevant for autism, schizophrenia, Alzheimer's disease, Parkinson's disease, and cognitive function. This data is an invaluable resource for identification of potential disease targets and biomarkers, as well as for elucidating the mechanism of action for neurological disorders and drugs targeting the CNS. The existing TRAP datasets cover three general areas: 1. Baseline data, collected from unperturbed transgenic bacTRAP mice, targeting specific cell types (neuronal, glial, microglial) in several brain regions (cortex, striatum, thalamus, hippocampus, hypothalamus). 2. Data from disease model studies (Alzheimer's disease, schizophrenia). 3. Data from MOA studies with existing or newly developed drugs for neurological disorders (schizophrenia, autism, Parkinson's Disease). In order to make best use of these existing datasets, we are making these data available to the greater neuroscience community. In addition to the microarray and RNAseq data, we have access to many Rockefeller TRAP lines which have been extensively backcrossed by us to the Bl6/J mouse strain, and a number of new bacTRAP transgenic lines generated in-house. The lines can be obtained from Jackson labs either through an MTA with Rockefeller University, or an MTA with Takeda Pharmaceuticals. Details of data and transgenic mouse lines will be available at this poster session.

Disclosures: **J.P. Doyle:** A. Employment/Salary (full or part-time):; Takeda California, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property rights/patent holder. **J.A. Vekich:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **K. Bobkov:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **C.S. Holub:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **D. Das:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **R. Yamashita:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **M. Ekstrand:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **A. Amador:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **E. Boshoff:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **P. Taskar:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **H. Schiffer:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **J. Atienza:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **J. Serrats:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **N. Chen:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **E. Yoo:** A. Employment/Salary (full or part-time):; taked. **G. Corbett:** A. Employment/Salary (full or part-time):; Takeda Cambridge. **J. Powell:** A. Employment/Salary (full or part-time):; Takeda Cambridge. **N. Brice:** A. Employment/Salary (full or part-time):; Takeda Cambridge. **N. Kaushal:** A. Employment/Salary (full or part-time):; Takeda California, Inc. **W.J. Ray:** A. Employment/Salary (full or part-time):; Takeda California, Inc..

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.08/JJJ39

Topic: I.02. Systems Biology and Bioinformatics

Support: R01 DC009977
T15 LM007056

Title: Integrating gene and protein data into SenseLab databases for neuroinformatics-driven discovery

Authors: *M. SURLES-ZEIGLER[1], T. M. MORSE[3], R. A. MCDOUGAL[2], G. M. SHEPHERD[4]
[1]Ctr. for Med. Informatics, [2]Neurosci., Yale Univ., New Haven, CT; [3]Neurosci., Yale Univ. Sch. Med., New Haven, CT; [4]Dept. Neurosci., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Neurons are often categorized by their wide range of properties, including, but not limited to, their morphology, location, and physiology. It is often challenging to identify commonalities and differences between these cells because individual papers and/or databases

frequently tend to focus on a single property. To solve this problem, NeuronDB (senselab.med.yale.edu/neurondb) has been created to aggregate neuronal information from multiple resources; this facilitates the integration and comparison of various cell types and properties for building computational models. NeuronDB currently provides unique tools to enable users to integrate data about the spatial expression of receptors and channels in individual neurons. Adding gene and protein expression data to the database is essential to increase understanding and comparison of neurons. We have begun to address this need with a data acquisition protocol, focusing on highly studied cells, initially cells of the hippocampus (cells of the dentate gyrus and regions CA1, CA3, and CA4). We systematically searched PubMed for combinations of cell types and well-known techniques. Papers and abstracts meeting a set of inclusion criteria were manually reviewed to identify the gene and protein expression data and the associated metadata (species, species strain and age, and technique used to identify data). This data is now available through NeuronDB and an interactive microcircuit viewer. This microcircuit viewer enables interoperability between the SenseLab databases' (e.g., NeuronDB, ModelDB) neuronal properties, with links to other properties such as electrophysiological data as tracked by associated databases such as Neuroelectro (http://neuroelectro.org). We will demonstrate this incorporation of protein and gene expression data into NeuronDB and show how it can accelerate basic science and modeling research, assisting in the exploration of experimental studies and models of neurons and their ion channels and receptors.

Disclosures: M. Surles-Zeigler: None. **T.M. Morse:** None. **R.A. McDougal:** None. **G.M. Shepherd:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.09/DP15/JJJ40

Topic: I.02. Systems Biology and Bioinformatics

Support: AG056236
NS047101

Title: A novel high-content platform for evaluation of dendritic spines in late-stage preclinical drug discovery

Authors: C. A. SHANKULA[1], J. K. ALEXANDER[2], K. KORJENIC[1], *C. S. REX[3]
[1]Afraxis, Inc., San Diego, CA; [2]Alexander Scientific Analysis and Programming, L.L.C., Austin, TX; [3]Dept of Neurobio., Afraxis Inc., San Diego, CA

Abstract: CNS drug discovery imposes unique barriers to rational drug evaluation - central to these are a lack of fundamental understanding of information processing in brain that gives rise

to affective and cognitive states. It is expected that these states emerge from the coordinated activities of individual synaptic contacts within and across distributed brain regions. Therefore, phenotypic analyses of synpatic activities should simultaneously assess broadly and at high resolution (single synapses). Here we describe the development of a scalable platform technology to evaluate individual dendritic spine morphometries from neuroanatomically precise samples across large numbers of distributed neurons within intact mammalian brain. We introduce a novel seeded image segmentation analysis method for semi-automated morphometry conducted on Airyscan super-resolution micrographs. This approach permits acquisition of >10,000 dendritic spines per animal within a reasonable cost-per-unit and timeframe for drug discovery. As a proof-of-principle, we evaluated the effects of low doses of ketamine on broadly distributed dendritic spines in young adult mice and rats, including locii of previously established effects (e.g. medial prefrontal cortex). We confirmed and optimized segmentation results against human observer results. We also introduce a novel statistical tool for nested parametric evaluation of non-parametric, multi-dimensional distributions of fundamental dendritic spine measures. This approach, we believe, will increase the reproducibility of dendritic spine analysis as well as permit assessment of inter-animal variances from fundamental morphometric measures - both advances are likely necessary for drug screens using dendritic spine analysis. Together, the novel assemblage of optimized assay utilities form a powerful late-stage preclinical CNS drug evaluation tool that can be deployed to probe responses of broadly distributed individual synapses in conjunction with in vivo pharmacology and introduce a level of scalability to whole animal drug testing that is typically reserved for high-throughput or high-content analysis.

Disclosures: C.A. Shankula: A. Employment/Salary (full or part-time):; Afraxis, Inc. **J.K. Alexander:** A. Employment/Salary (full or part-time):; Alexander Scientific Analysis and Programming, L.L.C. **K. Korjenic:** A. Employment/Salary (full or part-time):; Afraxis, Inc. **C.S. Rex:** A. Employment/Salary (full or part-time):; Afraxis, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Afraxis, Inc..

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.10/JJJ41

Topic: I.02. Systems Biology and Bioinformatics

Support: Simons Foundation #275724
R01 MH076431
U01 MH109501

Title: Predicting pathogenicity of structural variation in neurodevelopmental disorders using machine learning

Authors: *P. TANDON, O. SHANTA, D. ANTAKI, W. BRANDLER, M. KLEIBER, O. HONG, J. SEBAT
Psychiatry, UCSD, San Diego, CA

Abstract: Structural Variants (SVs) are genetic mutations that consist of changes in the copy number or arrangement of DNA sequences (> 50 bp) and include deletions, duplications, and inversions. Previous studies have shown that gene-disrupting SVs contribute to elevated risk for a variety of neurodevelopmental disorders including Autism Spectrum Disorders (ASD), Developmental Disorders (DD), and schizophrenia (SCZ) (Malhotra and Sebat 2012; Walsh et al. 2008). Despite continued success in identifying SVs that confer risk, current analytical approaches have been limited to investigations of the genome-wide burden of SVs or the enrichment of large gene-disrupting SVs at individual loci. Limited progress has been made in identifying smaller causal variants within individual genes or in regulatory regions of the genome that may affect risk.

This study seeks to develop more accurate pathogenicity prediction and functional interpretation tools for SVs using an integrative machine learning approach. The study develops a machine learning pipeline to fuse multiple biological functional annotations into a single pathogenicity score for a structural variant to assess risk for neurodevelopmental disorders. The trained classifier can distinguish deleterious SVs from neutral variants on a variety of data types including next-generation, whole genome sequencing, and clinical microarray data. On National Institute of Health (NIH) ClinVar data, the trained predictor can leverage multiple functional constraint predictors to predict the pathogenicity of an SV accurately, even in the absence of any previously-implicated highly-constrained gene (i.e. ExAC probability loss of function (pLI) score = 0.5).

The developed SV pathogenicity scoring system is used to investigate the unexplained genetic basis of psychiatric disease in SCZ and ASD. The predictor is more accurate than previous methods for scoring medium to large (10^5-10^6 bp) deletions in the Psychiatric Genomics Consortium (PGC) data (Wilcox $p < 0.01$). Emphasis in our study is placed on exploring the contribution of SVs that overlap non-coding regulatory elements to disease risk. The predictor utilizes fetal brain enhancer and promoter annotations (derived from Epigenetic Roadmap Project data) in an explicit non-coding classifier to improve prediction performance for non-exonic SVs. On Simons Simplex Consortium (SSC) data, our approach improves significance for non-coding variants in ASD patients (Wilcox $p < 0.01$).

Disclosures: P. Tandon: None. **O. Shanta:** None. **D. Antaki:** None. **W. Brandler:** None. **M. Kleiber:** None. **O. Hong:** None. **J. Sebat:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.11/JJJ42

Topic: I.02. Systems Biology and Bioinformatics

Support: A part of this work was supported by RIKEN Neuroinformatics Japan Center (NIJC).
Computational transformation work was mainly performed in Brain Atlas Ideathon/Hackathon and NIJC Hackathon organized by NIJC.
BrainTx and ViBrism DB are supported by the grant from RIKEN NIJC.
WHS MR images were provided from INCF Waxholm Space Task Force of the Program on Digital Brain Atlasing.
ISH image production of BrainTx was supported by JSPS KAKENHI 23300137 and 258057 to TF.
ViBrism DB was supported by JSPS KAKENHI 25560428, 26280110, 268032, 15HP8038, 16HP8032, and 17HP8082; and the RIKEN Strategic Programs for R&D to YO.
Development of the program was supported by Grant-in-Aid for JSPS Fellows 16J09788 to DM and JSPS KAKENHI 25330342 to HI.

Title: 2D/3D image integration on the BAH viewer

Authors: *Y. OKAMURA-OHO[1,2,3], D. MIYAMOTO[4], H. IKENO[5], M. MORITA[2], H. YOKOTA[2], S. WEMLER[6], A. SATO[7], T. FURUICHI[7], Y. OKUMURA[8], Y. YAMAGUCHI[8]
[1]Jissen Women's Univ., Hino-shi/Tokyo, Japan; [2]RIKEN Ctr. for Advanced Photonics, Wako, Japan; [3]BReNt-Brain Res. Network, Zushi-shi, Japan; [4]The Univ. of Tokyo, Tokyo, Japan; [5]Univ. of Hyogo, Himeji, Japan; [6]Wemler Software, Tokyo, Japan; [7]Tokyo Univ. of Sci., Noda, Japan; [8]RIKEN Ctr. for Brain Sci., Wako, Japan

Abstract: We introduce a web-based viewer for integration of two-dimensional (2D) *in situ* hybridization (ISH) images with three-dimensional (3D) gene expression image datasets located in the standard MRI coordinate. We configurated the viewer for 2,810 para-sagittal sectioned mouse brain ISH images of the BrainTx database (http://www.cdtdb.neuroinf.jp), 3D gene expression image datasets, which were made using a microtomy-based microarray assay system, Transcriptome Tomography, and archived in the ViBrism DB (http://vibrism.neuroinf.jp), and MR images of the mouse standard coordinate space, Waxholm space (WHS, https://www.nitrc.org/projects/incfwhsmouse). Each ISH image was linearly transformed into each of a series of para-sagittal MR image slices of the WHS, and he best-fit slice were identified by calculating the similarity metric value (δ). We parallelized this computation framework, using the IPython cluster package, and implemented it on the PC cluster provided for the Brain

Atlasing Hackathon (BAH) activity hosted by Neuroinformatics Japan Center in Japan. Transformed 2D images to the best-fit MR image were visualized in the BAH viewer using a Web-GL based back-projection methods along with 3D gene expression images of ViBrism DB. Three types of data, produced with different modalities and originally located in different dimensions, were successfully compared in the viewer.

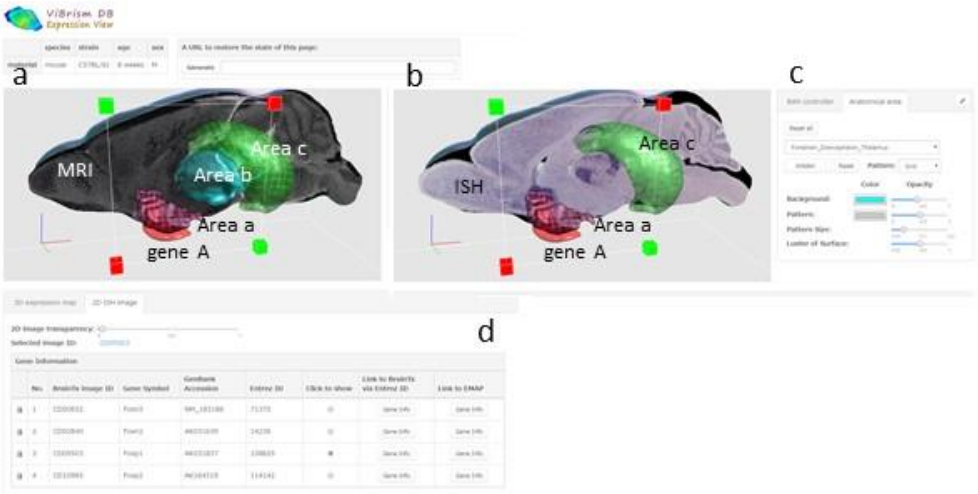


Fig.1 Example views of images in BAH Viewer and BAH control panels

a. a 3D expression map of gene A and anatomical areas a, b, and c of WHS are shown in a para-sagittal plain image of WHS MRI.
b. a 2D ISH image is superimposed on the MR image along with maps of the gene A and the area a.
c. the BAH controller and Anatomical area selection tabs
d. 2D ISH images and 3D expression map images selection tabs

Disclosures: Y. Okamura-Oho: None. **D. Miyamoto:** None. **H. Ikeno:** None. **M. Morita:** None. **H. Yokota:** None. **S. Wemler:** None. **A. Sato:** None. **T. Furuichi:** None. **Y. Okumura:** None. **Y. Yamaguchi:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.12/JJJ43

Topic: I.02. Systems Biology and Bioinformatics

Title: *In vivo* morphological imaging of brain cancer using Gaussian weighted Laplace prior regularization

Authors: H. HUI[1], X. YANG[1], *J. TIAN[2]
[1]Key Lab. of Mol. Imaging, CAS, Inst. of Automation, Chinese Acad. of Scienc, Beijing, China; [2]Key Lab. of Mol. Imaging, CAS, Beijing City, China

Abstract: Bioluminescence tomography (BLT) is a powerful non-invasive molecular imaging tool for in vivo studies of glioma in mice. However, because of the light scattering and resulted ill-posed problems, it is challenging to develop a sufficient reconstruction method, which can accurately locate the tumor and define the tumor morphology in three-dimension. In this work, we proposed a novel Gaussian weighted Laplace prior (GWLP) regularization method. It considered the variance of the bioluminescence energy between any two voxels inside an organ had a non-linear inverse relationship with their Gaussian distance to solve the over-smoothed tumor morphology in BLT reconstruction. We compared the GWLP with conventional Tikhonov and Laplace regularization methods through various numerical simulations and in vivo orthotopic glioma mouse model experiments. The in vivo magnetic resonance imaging (MRI) and ex vivo GFP fluorescent images and H&E stained images of whole brain cryoslicing specimens were utilized as gold standards. The results demonstrated that GWLP achieved the highest accuracy in tumor localization and tumor morphology preservation. This study achieved accurate BLT morphological reconstruction of orthotopic glioma without using any segmented tumor structure from any other structural imaging modalities as the prior for reconstruction guidance. This enabled BLT more suitable and practical for in vivo imaging of orthotopic glioma mouse models.

Disclosures: H. Hui: None. **X. Yang:** None. **J. Tian:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.13/JJJ44

Topic: I.02. Systems Biology and Bioinformatics

Support: NSF Grant 1516527
BMBF Grant 01GQ1302
BMBF Grant 01GQ1509
Project LO1506 of the Czech Ministry of Education, Youth and Sports under the program NPU I

Title: Using the open metadata Markup Language (odML) and Semantic Web methods to facilitate interoperability of diverse neurophysiology data

Authors: *J. L. TEETERS[1], P. JEŽEK[2], M. SONNTAG[3], Y. SHALIVSKYY[3], A. KOUTSOU[3], J. GREWE[4], F. T. SOMMER[1], T. WACHTLER[3]
[1]Redwood Ctr. for Theoretical Neurosci., UC Berkeley, Berkeley, CA; [2]Dept. of Computer Sci. and Engin., Univ. of West Bohemia, Pilsen, Czech Republic; [3]G-Node, Dept. Biol. II, Ludwig-Maximilians-Universität München, Planegg, Germany; [4]Inst. for Neurobio., Eberhard-Karls-Universität, Tübingen, Germany

Abstract: In order to efficiently find and use shared scientific data, the metadata describing the data must be detailed and standardized to be machine readable. Currently, for neurophysiology data, this is often not the case. Many labs still use custom formats to store data. Multiple standardized formats (such as Kwik [1], NEO [2], NIX [3] and NWB [4]) have been recently developed which store metadata in a consistent manner. However, the diversity of the experiments often requires metadata elements that are not included in any existing standard. Moreover, neurophysiology metadata are still stored in a multitude of incompatible formats, and thus cannot be processed consistently by software tools.
As a step towards solving the problem of diversity in metadata representation, we present an approach which combines the use of the open metadata Markup Language (odML) [5] with Semantic Web methods. The approach was developed using datasets stored in CRCNS.org and the G-Nodes's GIN [6] data repositories and can be used by labs and data repositories to make their shared data easier to find and interoperable between datasets and repositories. The odML format is highly suitable for representing metadata from heterogeneous datasets, because it provides a standardized, machine-readable representation of metadata without constraining the content. While converting metadata to odML puts the metadata in a common format, there can still be differences between datasets in the organization of the same type of metadata within the odML structure. To reduce these differences we proposed and provided odML Terminologies [7] as optional templates for common metadata use cases. The Semantic Web methods are harnessed through software we have developed which converts odML-formatted metadata to the Semantic Web Resource Description Framework (RDF) data model. The RDF representation allows metadata from multiple sources to be combined into a common graph and searched using the SPARQL query language, and thus facilitates interoperability of diverse neurophysiology data across repositories.
[1] http://klusta.readthedocs.io/en/latest/kwik/
[2] http:neuralensemble.org/neo/
[3] http://www.g-node.org/nix
[4] nwb.org
[5] http://www.g-node.org/odml
[6] https://web.gin.g-node.org
[7] https://github.com/G-Node/odml-terminologies

Disclosures: J.L. Teeters: None. **P. Ježek:** None. **M. Sonntag:** None. **Y. Shalivskyy:** None. **A. Koutsou:** None. **J. Grewe:** None. **F.T. Sommer:** None. **T. Wachtler:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.14/JJJ45

Topic: I.02. Systems Biology and Bioinformatics

Title: KRSA: A user-friendly tool for identifying significant differences in kinase activity from kinome array data

Authors: *E. DEPASQUALE[1,3], E. BENTEA[2,1], N. NAWREEN[2,1], J. L. MCGUIRE[2,1], J. MELLER[3,1], R. E. MCCULLUMSMITH[2,1]
[2]Psychiatry and Behavioral Neurosci., [1]Univ. of Cincinnati, Cincinnati, OH; [3]Biomed. Informatics, Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

Abstract: As an important mechanism of post-translational modification, phosphorylation by serine/threonine kinases is critical for altering protein function. In order to examine differences in kinase activity on a large scale, kinase substrate arrays (or kinome arrays) have been developed that allow for testing of differential phosphorylation between conditions across many different serine/threonine kinases. We utilized the kinome array platform to discover differences in kinase activity from dorsolateral prefrontal cortex (DLPFC) between male (n=3) and female (n=3) subjects, with a sliding fold change cutoff for identifying significantly different peptide phosphorylation levels. As a replication study, DLPFC from control males (n=10), control females (n=10), schizophrenia males (n=10), and schizophrenia females (n=10) were pooled by group and kinase activity was assessed using the kinome array. To identify which kinases were targeting these peptides, we developed a new application: Kinome Random Sampling Analyzer (KRSA) using the Shiny platform in R. This application takes mappings of protein kinases predicted to target the peptides used in the kinome array from publicly-available databases, enforces optional quality control constraints on the data, then performs resampling analysis to identify kinases that phosphorylate the peptides at a greater frequency than would be expected by chance. From the KRSA results, signaling network models linking the kinases identified in the resampling analysis were constructed using known interactions in the Ingenuity database. Previous studies performed in our laboratory using KRSA confirmed the predictive accuracy of the method through PCR, western blots, and kinome arrays with inhibitors of the affected kinases. Through these studies, significant kinase activity differences between males and females in both unaffected brain tissue and affected tissue were identified and the intersection between the two phosphorylation networks was examined to glean knowledge on how sex differences may play a role in the molecular underpinnings of disease.

Disclosures: E. Depasquale: None. **E. Bentea:** None. **N. Nawreen:** None. **J.L. McGuire:** None. **J. Meller:** None. **R.E. McCullumsmith:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.15/JJJ46

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH grant OD011190

Title: New and improved CrePortal, a comprehensive recombinase expressing mice resource at Mouse Genome Informatics (MGI: www.infomatics.jax.org)

Authors: *H. ONDA, E. S. MAYOTTE, L. BECHTEL, S. A. MURRAY, C. L. SMITH
Mouse Genome Informatics, The Jackson Lab., Bar Harbor, ME

Abstract: Since the introduction in early 1980s, over 20,000 “conditional-ready” mice containing recombinase recognition sites have been generated. The technology is based on the mutant mice expressing site specific recombinase, notably Cre, but also Flp, Dre, phiC31, paired with mice containing two DNA recognition sites in their genome. To realize full utility of those “conditional ready” mice, spatial and temporal specificity of recombinase activities in cognate recombinase-driver mice need to be fully characterized. There have been large bodies of published results indicating recombinase activities in the intended tissue or cell type. However, negative results or spurious activities of those recombinase in other tissues or time points are often overlooked or omitted from reporting, thus not easily available to potential users in search of appropriate recombinase driver lines. The CrePortal (*www.informatics.jax.org/home/recombinase*) catalogues published and unpublished researcher-submitted recombinase driver mouse lines to facilitate identification of the most suitable mouse lines for conditional mutagenesis experiment by providing a centralized, comprehensive set of well-annotated recombinase driver mouse lines in easy to search database. It currently provides data for over 2,900 transgenes and knock-in recombinase driver alleles. Recombinase activity is annotated not only on its reported activity, but also for activity not-detected. We have improved the database in our new release by enabling a search for mice with activities detected in specific anatomical structure and nowhere else. In addition to this new search capability, the recombinase summary now displays a new matrix of gene expression data and recombinase activity data side-by-side to easily visualize comparison of endogenous driver expression and reported recombinase activities in various structures/tissues. The search results summary page now shows sortable columns of: a list of drivers, icon linking to matrix views, allele symbols, organ systems activity detected, organ systems activity not detected, inducing agent, link to International Mouse Strain Resource (IMSR, *www.findmice.org*), link to references, and allele synonym(s). Here, we describe new features found in the CrePortal from the Mouse Genome Informatics (MGI,

www.informatics.jax.org), and encourage you to explore this resource for recombinase allele information for the scientific community.

Disclosures: H. Onda: None. **E.S. Mayotte:** None. **L. Bechtel:** None. **S.A. Murray:** None. **C.L. Smith:** None.

Poster

698. Systems Biology and Bioinformatics: Bioinformatics

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 698.16/JJJ47

Topic: I.02. Systems Biology and Bioinformatics

Support: NSF US IGNITE, 10037840

Title: The international neuromodulation registry: A graph database representation of patient-specific data with combined predictive modeling for neuromodulation therapies

Authors: *D. HEDGES[1], G. DUFFLEY[3], R. GOURIPEDDI[2], C. R. BUTSON[1]
[1]SCI Inst., [2]Biomed. Informatics, Univ. of Utah, Salt Lake City, UT; [3]Bioengineering, Univ. of Utah Dept. of Bioengineering, Salt Lake City, UT

Abstract: Neuromodulation therapies such as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS) have provided symptomatic relief and improved quality of life for certain patients with movement disorders and psychiatric conditions. Unfortunately, the effects of neuromodulation therapies can be highly variable and difficult to quantifiably predict for individual patients. To enhance the accuracy of predictive models, we have created a novel, metadata-driven informatics mechanism to incorporate data from hundreds of patients into predictive computational models. This platform is integrated into the International Neuromodulation Registry, housed at the University of Utah. Within the framework of this patient registry, this informatics platform provides the means to quantitatively combine seemingly disparate data types such as neuroimaging, genetics, demographics, and rating scales for both quality of life and disease severity. The data are organized using the Neo4j graph database management system and can either be uploaded from the University of Utah electronic medical record or from external collaborators. In addition to storing and allowing data retrieval, this system can display and discover complex data relationships. We have paired this database with an analysis pipeline that generates patient specific models of deep brain stimulation (DBS). When data from a patient is uploaded into the registry, a computational model of the patient's DBS implant is generated and sent back to the user. The user can then explore the model via an iOS device such as an iPad, using ImageVis3D Mobile, an app freely available from the iTunes App Store. The model contains individual patient imaging, anatomy, and predictions of the volume of tissue activated (VTA). The model allows the clinician to adjust simulation settings

and visualize the spatial changes of activation from both 2D and 3D views. Given the potential for this platform to improve both translational research and patient care via data-driven predictive analysis, we believe that this next-generation clinical database will play a pivotal role in advancing the field of neuromodulation.

Disclosures: G. Duffley: None. **R. Gouripeddi:** None. **C.R. Butson:** F. Consulting Fees (e.g., advisory boards); NeuroPace, Advanced Bionics, Boston Scientific, Intelect Medical, Abbott (St. Jude Medical), Functional Neuromodulation.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.01/JJJ48

Topic: I.04. Physiological Methods

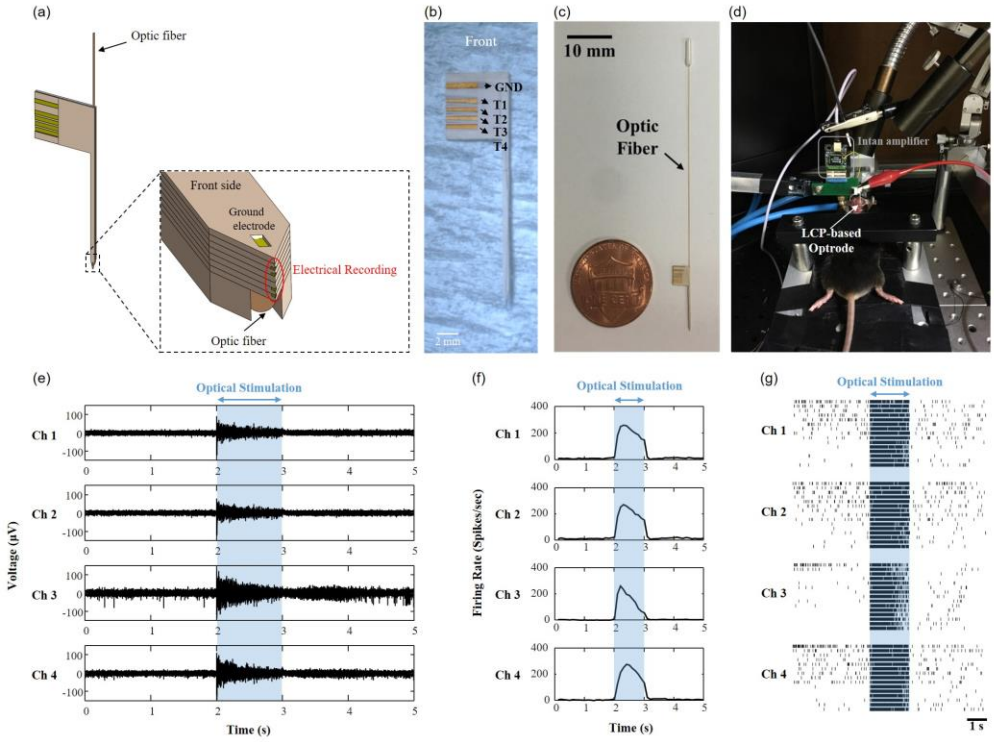
Support: Defense Acquisition Program Administration Grant UD170030ID

Title: Liquid crystal polymer-based multichannel depth probe with polymeric optical fiber for optogenetic stimulation and electrical recording of CaMKIIα expressing CA1 pyramidal cells of mouse

Authors: C. KIM[1], S. SHIN[1], J.-H. KIM[2], S.-H. LEE[2], *S. KIM[1]
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]KAIST, Daejeon, Korea, Republic of

Abstract: With optogenetic approach, genetically modified target cells can be stimulated or inhibited in timescale of millisecond, which is ideal for studying brain circuitry. For optogenetic stimulation and simultaneous electrical recording, we developed a depth probe comprising a liquid crystal polymer (LCP)-based tetrode and a polymeric optical fiber.
The LCP-based tetrode has four working electrodes at the tip of the shank, a ground electrode at the front of the shank, and a polymeric optical fiber at the back of the shank. The tetrode was fabricated using MEMS process, thermal lamination, and laser machining. The dimension of the shank is 300μm-thickness, 300μm-width, and 10mm-length. The electrodes were fabricated by electroplating gold. The working electrodes was shaped as two adjoining rectangles having size of 10μm-thickness and 50μm-width. The average electrical impedance of the working and ground electrode of 10 fabricated devices were 161+67kΩ and 10.3+3.3kΩ. The polyimide-coated, multi-mode optical fiber with diameter of 125μm was buried in the back side of the tetrode. For the optogenetic experiment, mouse transgenic line of CaMKIIa-cre and DIO-ChR2-EYFP were mated to produce transgenic line of CaMKIIa-ChR2-EYFP. The fabricated optrode was inserted to hippocampal CA1 area and blue laser (473nm wavelength) with power of 1.5mW was irradiated through the optical fiber. The electrical signal was recorded at working electrodes using Intan amplifier. The raw trace was further processed to get the peri-stimulus time

histogram and rastor plot. The result clearly showed the optogenetic experiment was successful. In summary, we developed the LCP-based optrode having four working electrodes at the tip of the shank, and successfully conducted optogenetic experiment on CA1 pyramidal cells using the fabricated optrode. We are currently developing the LCP-based optrode to have more number of electrodes and the distance from the electrodes to be close to the tip of optical fiber.
*Chaebin Kim, Soowon Shin, and Jae-Hyun Kim are equally contributed to this work.



Disclosures: C. Kim: None. **S. Shin:** None. **J. Kim:** None. **S. Lee:** None. **S. 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.; Research supported in part by the BK21 Plus Project, Department of Electrical and Computer Engineering, SNU, in 2018; and in part by a grant to CABMC (Control of Animal Brain using MEMS Chip) project.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.02/JJJ49

Topic: I.04. Physiological Methods

Support: NIH U01 NS099573

Title: All-optical screening of near-infrared genetically encoded voltage indicators

Authors: M. MATLASHOV[1], *C. SONG[2], M. COLAVITA[2], M. MONAKHOV[3], D. M. SHCHERBAKOVA[1], S. D. ANTIC[4], V. V. VERKHUSHA[1], T. KNOPFEL[2]
[1]Anat. and Structural Biol., Albert Einstein Col. of Med., Bronx, NY; [2]Med., Imperial Col. London, London, United Kingdom; [3]Neurosci., Uconn Hlth., Farmington, CT; [4]Neurosci, UConn Hlth., Farmington, CT

Abstract: Development of better performing genetically encoded voltage indicators (GEVIs) has been ongoing for the last several decades, yet its progress is limited by the low throughput of testing rationally designed new variants and screening high diversity libraries. Currently, single cell patch-clamp electrophysiology provides excellent data quality, and field stimulation techniques have reasonable throughput. We recently developed near-infrared (NIR) GEVIs that can be combined with blue light-controlled optogenetic membrane voltage actuation. This opens the path for an efficient all-optical screening approach for optimisation and evolution of new NIR GEVI variants. We generated a human embryonic kidney 293 (HEK293) cell line that constitutively expresses the blue-shifted cation channel opsin CheRiff (to enable a blue-light stimulation) and the potassium channel Kir2.1 (to achieve a sufficiently negative baseline membrane potential). Using patch-clamp electrophysiology, we verified that flashes of blue light drive the membrane potential from a baseline level (about -90 mV) close to the opsin reversal potential (about 0 mV). Transient expression of NIR GEVI variants in this cell line allowed determining their voltage sensitivity using an all-optical technique. Based on the same principle, we tested a series of NIR GEVI variants that emerged from the HEK293 cell-based screening in primary neuronal cultures. Action potentials were evoked either by a current injected through the patch-clamp pipette or by a CheRiff-mediated photocurrent. Cell-to-cell and construct-to-construct variations of the action potential-reporting optical signal were comparable between the two stimulation methods. All-optical testing largely increased the throughput of this secondary screening method. This screening approach can now be applied in multi-well format and microfluidics approaches.

Disclosures: M. Matlashov: None. **C. Song:** None. **M. Colavita:** None. **M. Monakhov:** None. **D.M. Shcherbakova:** None. **S.D. Antic:** None. **V.V. Verkhusha:** None. **T. Knopfel:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.03/JJJ50

Topic: I.04. Physiological Methods

Support: National Institute of Neurological Disorders and Stroke 5R01NS086804
NSF CBET-1253890
Center for Sensorimotor Neural Engineering EEC-1028725
McGovern Institute for Brain Research at MIT

Title: Multifunctional neural probe development via thermal drawing

Authors: *A. CANALES[1], S. PARK[1], M.-J. ANTONINI[1], C. LU[2], P. ANIKEEVA[1]
[1]MIT, Cambridge, MA; [2]Applied Materials, Santa Clara, CA

Abstract: Seamless integration of neural probes still presents many challenges despite advances in the materials and fabrication methods used. This is particularly relevant when combining multiple modalities of interacting with the brain, such as electrical recording and stimulation, and optical stimulation. Bi-directional communication with the brain, however, is crucial in furthering our knowledge of neural circuits in health and disease.
In order to address these challenges, we have used a thermal drawing process to develop multifunctional neural probes. Using soft materials, such as polymers and composites, and metals, we have fabricated flexible probes that provide co-localization of the different functionalities included. These probes can be used to record neural activity, for optical stimulation, and to deliver drugs or viruses at a region of interest. Furthermore, these probes have been successfully used in both the brain and the spinal cord of mice.
Using one of these probes, we developed a one-step optogenetics procedure. In this process, the virus carrying the gene expressing the light-sensitive protein was injected using the same device that was later used to provide the optical stimulation, and to record the neuronal response. These measurements were done in freely behaving mice, and we were able to observe changes in mice behavior correlated with the optical stimulation. These probes were able to record single unit activity, and to track it over at least 3 months.
We have also used elastomers to fabricate a stretchable probe. The mechanical flexibility of these probes makes them suitable to be used in environments with large amount of moving and stretching, such as the spinal cord. We used these probes to optically stimulate and record neural activity from the spinal cord of freely moving mice. We also correlated the electromyography measured in the leg to the optical stimulus delivered in anesthetized mice.

Disclosures: A. Canales: None. **S. Park:** None. **M. Antonini:** None. **C. Lu:** None. **P. Anikeeva:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.04/JJJ51

Topic: I.04. Physiological Methods

Title: Long-term time-lapse observation of cells with photo-stimulation by using portable *in vitro* cell imaging system

Authors: *A. KIMURA[1], M. HARUTA[2], T. NODA[2], K. SASAGAWA[2], T. TOKUDA[2], J. OHTA[2]
[1]Materials Science, Grad. Sch. of Sci. and Technol., [2]Materials Sci., Nara Inst. of Sci. and Technol., Ikoma / Nara, Japan

Abstract: As neuronal migration is crucial for brain development, unveiling its mechanism contributes to understanding of neurodevelopmental disorders. To observe behavior of cells *in vitro*, we have developed a portable *in vitro* cell imaging system based on a direct contact imaging by using a CMOS image sensor. To acquire bright field images of cells, we just directly put a culture dish on a CMOS image sensor of this imaging system. The developed imaging system is integrated with green and blue LEDs. When bright field images are acquired, The green LED is used to acquire bright field images illuminated, while the blue LED is used to stimulate cells optically. The size of the CMOS image sensor is so large that it can take image in a large area without sifting it. In addition, the package of this imaging system is so compact that it can be laid in typical CO_2 incubators without removing the shelf.
By using this portable *in vitro* cell imaging system, we first observed behavior of Neuro2a cells under normal condition. To observe cellular migration, we performed scratch wound healing assay and we could acquire the time-lapse images of cellular migration. Next, we transfected Channelrhodopsin 2 to Neuro2a cells and performed time-lapse imaging of scratched dish under photo-stimulated condition. We successfully acquired the time-lapse images of cellular migration, and the behavior of cells was almost the same as in the normal condition. In addition, apoptosis was not observed, suggesting that the LED light intensity is not harmful to cells and suitable for photo-stimulation.
The combination of this portable *in vitro* cell imaging system and light-sensitive channels can help to reveal the migration mechanism in future.

Disclosures: A. Kimura: None. **M. Haruta:** None. **T. Noda:** None. **K. Sasagawa:** None. **T. Tokuda:** None. **J. Ohta:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.05/JJJ52

Topic: I.04. Physiological Methods

Support: BB/M02556X/1

Title: Fast-decay red fluorescent genetically-encoded calcium indicators

Authors: *S. KERRUTH, C. COATES, K. TÖRÖK
Mol. and Clin. Sci. Res. Inst., St George's, Univ. of London, London, United Kingdom

Abstract: The time-course of intracellular Ca^{2+} transients is hard to assess due to buffering and signal integrating interactions. Genetically-encoded calcium indicators (GECI) have proven useful for monitoring Ca^{2+} transients in living cells and organisms. However, Ca^{2+} indicators with high Ca^{2+} affinity and slow decay kinetics themselves integrate Ca^{2+} signals, and furthermore may become saturated before peak [Ca^{2+}] is reached. Thus, for more faithful tracking of rapid Ca^{2+} dynamics, probes with faster off-kinetics are required[1,2]. Red-fluorescent GECI have been developed with the view of multicolour imaging and optogenetic applications[3]. Here we report novel fast-decay variants of red-fluorescent genetically-encoded Ca^{2+} indicators jRGECO1a and jRCaMP1a[3] with up to 8-fold ($t_{1/2}$ of 6.4 ms) and 13-fold ($t_{1/2}$ of 33 ms) faster *in vitro* decay kinetics (37 °C), respectively. Fast-decay jRGECO1a and jRCaMP1a variants retain comparable fluorescence brightness and dynamic range values to their parent proteins. The fluorescence dynamic range of the brighter mApple-based jRGECO1a variants is stable between pH 6.5 and 7.5, but declines above pH 7.5 to a Ca^{2+}-independent fluorescent state. In contrast, the less bright jRCaMP1a variants, based on mRuby, are stable over the pH range of 6.5 to 10. Red-fluorescent GECI, like their green-fluorescent counterparts, are characterised by high cooperativity to Ca^{2+}, and complex kinetic patterns of Ca^{2+}-dependent fluorescence response with a limiting *on*-rate. However, the fast-decay variants of jRGECO1a and jRCaMP1a reveal 8-fold faster ATP-evoked Ca^{2+} transients compared to their parent proteins in HEK293T cells, showing the benefits of fast-decay red-fluorescent GECI indicators for monitoring Ca^{2+} dynamics in living cells.

This work is funded by BBSRC grant BB/M02556X/1 to K.T.

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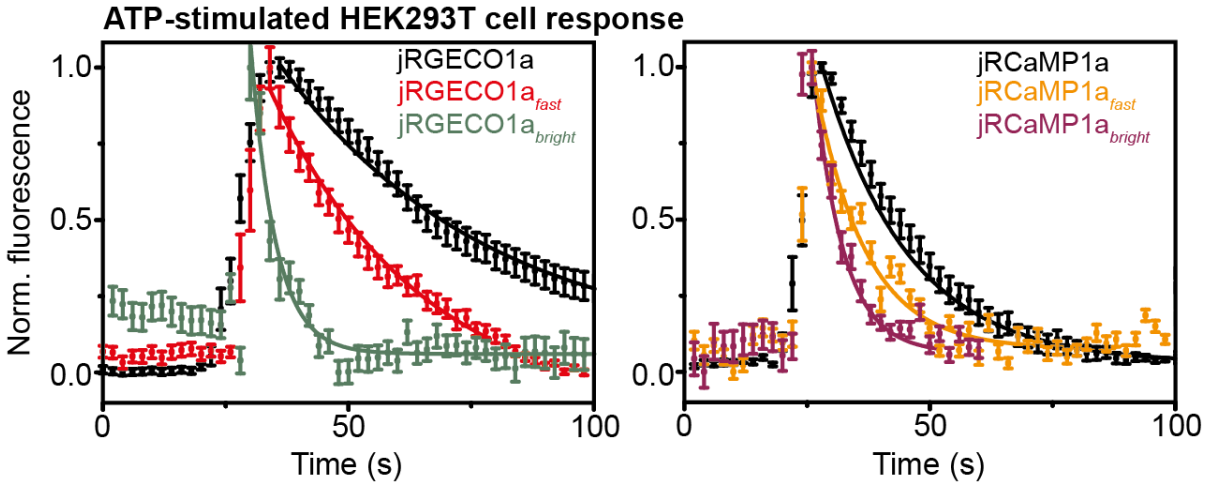

Disclosures: S. Kerruth: None. **C. Coates:** None. **K. Török:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.06/JJJ53

Topic: I.04. Physiological Methods

Support: ERC Grant 677683
ERC Grant 692943
NIH Grant U01NS094190
Simons Collaboration on the Global Brain Grant 543037SPI

Title: Fiber photometry at depth with tapered optical fibers

Authors: *F. PISANO[1], M. PISANELLO[1], E. MAGLIE[1,2], M. HYUN[3], A. BALENA[1,2], L. SILEO[1], M. DE VITTORIO[1,2], B. L. SABATINI[3], F. PISANELLO[1]
[1]Ctr. for Biomolecular Nanotechnologies, Italian Inst. of Technol., Arnesano, Italy; [2]Dept. di Ingegneria dell'Innovazione, Univ. del Salento, Lecce, Italy; [3]Dept. of Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Neuroscientists are paying increasing attention to fiber photometry techniques to record neural activity of genetically-targeted populations in behaving animals[1-3]. However, light scattering and absorption confine the recording volume addressed by conventional approaches to the vicinity of the fiber tip (~300μm). To circumvent this limitation, we propose tapered optical fibers (TFs) as photometry probes to collect fluorescent photons originated at depth. We measured light collection diagrams for TFs, TFs with micro-structured optical windows[4-6] and flat cleaved fibers (FFs) in semi-transparent and turbid medium. To do this, we used a two-photon microscope to measure the intensity collected by the waveguide surface when a focal spot is raster scanned in its proximity. We reconstructed the distribution of light delivered by the TF using a de-scanned pinhole imaging system. The combination of light collection and illumination diagrams led us to calculate the optical photometry efficiency of our devices. This led us to demonstrate that TFs collect photons from their whole optically active region, covering depths that depend on the fiber NA, core size and taper angle (Fig.1a). Despite collecting less photons overall, TFs are better suited than standard fibers to interface with extended and deep regions (Fig.1b). We also found that light collection can be localized to cellular volumes at specific depth by micro-structuring optical windows on the surface of TFs coated with a metallic layer (Fig.1c a diagram of the device and collection volumes of a 45 μm × 45 μm window as a function of the fraction of all collected photons). In light of these results, we view TFs as a complementary tool for fiber photometry experiments in cortical and sub-cortical regions.
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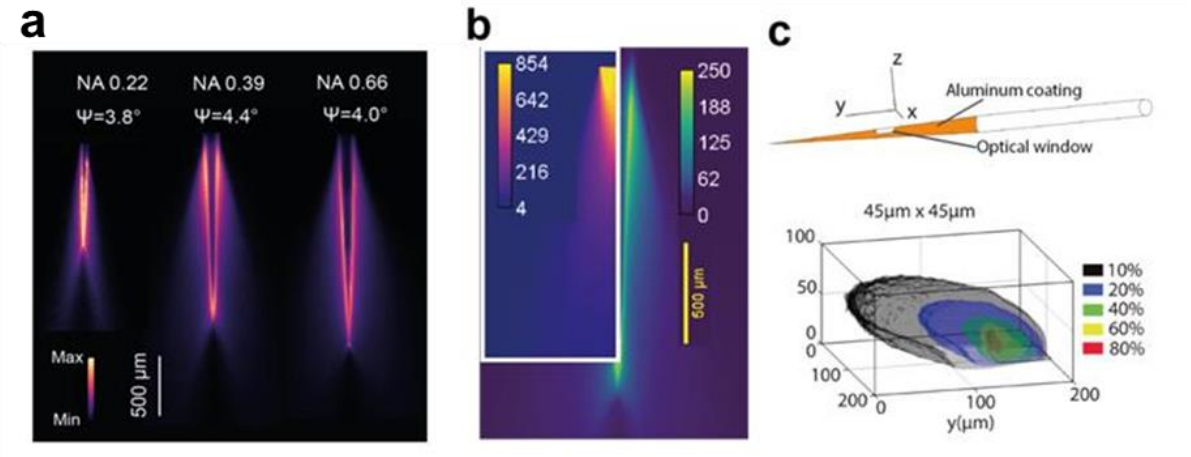

Disclosures: F. Pisano: None. **M. Pisanello:** None. **E. Maglie:** None. **M. Hyun:** None. **A. Balena:** None. **L. Sileo:** None. **M. De Vittorio:** None. **B.L. Sabatini:** None. **F. Pisanello:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.07/JJJ54

Topic: I.04. Physiological Methods

Support: BBSRC grant BB/M02556X/1
Wellcome Trust grant 094385/Z/10/Z

Title: Diverse mechanisms of glutamate sensing by chemically labelled and genetically encoded fluorescent protein probes

Authors: C. COATES, N. HELASSA, *K. TÖRÖK
SGUL, London, United Kingdom

Abstract: Protein-based fluorescent glutamate sensors have the potential for real-time monitoring of synaptic and cellular glutamate concentration changes. We have developed both genetically encoded and chemically labeled fluorescent glutamate sensors and characterised their mechanisms of glutamate sensing. Fluorescence enhancement of genetically encoded probes $iGlu_u$ and $iGlu_f$ (Helassa *et al*., *Proc. Nat. Ac. Sci. USA, in press* (bioRxiv 233494; doi:

https://doi.org/10.1101/233494)) is based on two flanking portions of the bacterial periplasmic glutamate/aspartate binding protein (GluBP) reattaching on glutamate binding and thereby correcting the structure of circularly permuted EGFP (Marvin *et al*., 2013). Apo-iGluSnFR has low fluorescence; to achieve a highly fluorescent state, reconstitution of GluBP is required, stabilized by bound glutamate. Ultrafast sensor iGlu$_u$ first binds glutamate, which is not sufficient for fluorescence enhancement. Binding is followed by a conformational change (the reattachment of GluBP fragments) during which the highly fluorescent state develops. This step limits the rate of the fluorescence response. A novel variant, iGlu$_m$ with mM affinity for glutamate, follows an alternative kinetic path whereby reattachment of GluBP fragments occurs first, accounting for 15% of the fluorescence enhancement; glutamate binding to the reformed complex causes 85% of the fluorescence enhancement. Fl-GluBP, a glutamate sensor generated by fluorescent derivatization of GluBP with a synthetic fluorophore yields 90% of its fluorescence enhancement in the initial glutamate binding phase. The rate of fluorescence response by Fl-GluBP is faster, with a diffusion limited rate constant. Thus, while iGlu$_u$ signals the glutamate *on*-process by a concentration-independent rate, iGlu$_m$ and Fl-GluBP fluorescence response rates are glutamate concentration-dependent. The *off*-rates of all three probes allow sub-millisecond detection, at 34 °C. Through their broad affinity range and mechanistic variety, the above selection of genetically encoded and chemically labeled fluorescent glutamate sensors are suitable for monitoring the different processes that glutamate undergoes in neurotransmission and cellular homeostasis.

Disclosures: C. Coates: None. **N. Helassa:** None. **K. Török:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.08/JJJ55

Topic: I.04. Physiological Methods

Support: BRAIN Initiative grant U01 NS094246

Title: Analyzing the two-photon absorption of red fluorescent genetically-encoded calcium ion indicators

Authors: *R. MOLINA[1], Y. SHEN[2], Y. QIAN[2], R. E. CAMPBELL[2], T. E. HUGHES[1], M. DROBIZHEV[1]
[1]Cell Biol. & Neurosci., Montana State Univ., Bozeman, MT; [2]Chem., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Genetically-encoded calcium ion indicators (GECIs) illuminate brain activity in model organisms. The basic design consists of a Ca2+ binding domain attached to a fluorescent protein

in such a way that the binding of Ca2+ modulates its fluorescence. The current favorite GECI is the green GCaMP6, due to the large increase of fluorescence upon binding Ca2+ (up to a 50-fold change). However, red fluorescence scatters less than green fluorescence, which is especially desirable for deeper imaging in tissue. Although there are red fluorescent GECIs available, they are less popular for reasons that include a smaller change in fluorescence. Three factors can contribute to the change in fluorescence: 1) different quantum yields of the Ca2+-bound and Ca2+-free forms; 2) different extinction coefficients or cross sections, in one- or two-photon imaging, respectively; and 3) a redistribution of the neutral and anionic forms of the chromophore in the presence of Ca2+. The third factor was previously shown to be the predominant mechanism for modulating the fluorescence of GCaMP6. We present a thorough analysis of the one-photon and two-photon properties of several red GECIs and use this data to determine the main factor(s) contributing to the increase in fluorescence upon binding Ca2+, particularly under two-photon excitation. In most cases we observe both the change of the maximum two-photon cross section and the shift of equilibrium between the neutral and anionic forms of the chromophore upon binding Ca2+. Quantitative analysis of the two-photon absorption properties can tell us about changes in the electrostatic environment around the chromophore and can potentially direct mutagenesis efforts towards creating red GECIs with a larger Ca2+-dependent fluorescence increase.

Disclosures: R. Molina: None. **Y. Shen:** None. **Y. Qian:** None. **R.E. Campbell:** None. **T.E. Hughes:** None. **M. Drobizhev:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.09/JJJ56

Topic: I.04. Physiological Methods

Support: NSFC Grant 21778034
NSFC Grant 31370822

Title: Sensing Ca^{2+} without perturbing neurons: The design, validation and applications of GCaMP-X

Authors: *X. LIU[1], Y. HE[2], Y. LIU[2], P. LI[1], S. YUE[1], Y. YANG[1,2]
[1]Beihang Univ., Beijing City, China; [2]Dept. of Biomed. Engin., Tsinghua Univ., Beijing, China

Abstract: GCaMP, one popular type of genetically-encoded Ca^{2+} indicators, has been associated with various side-effects. Here we unveil the intrinsic problem prevailing over different versions and applications, showing that GCaMP containing CaM (calmodulin) interferes with both gating and signaling of L-type calcium channels (Ca_V1). GCaMP acts as impaired apoCaM and

Ca^{2+}/CaM both critical to Ca_V1, which disrupts Ca^{2+} dynamics and gene expression. We then design and implement GCaMP-X, by incorporating an extra apoCaM-binding motif, effectively protecting Ca_V1-dependent excitation-transcription coupling from perturbations. GCaMP-X resolves the problems of detrimental nuclear accumulation, acute and chronic Ca^{2+} dysregulation, and aberrant transcription signaling and cell morphogenesis, while still demonstrating excellent Ca^{2+}-sensing characteristics partly inherited from GCaMP. In summary, CaM/Ca_V1 gating and signaling mechanisms are elucidated for GCaMP side-effects, while allowing the development of GCaMP-X to appropriately monitor cytosolic, submembrane or nuclear Ca^{2+} (Yang *et al.* Nature Communications 2018), which is also expected to guide the future design of CaM-based molecular tools. In addition, some recent progress in applying GCaMP-X to elucidate biophysical and physiological mechanisms in neurons will be discussed.

Disclosures: X. Liu: None. **Y. He:** None. **Y. Liu:** None. **P. Li:** None. **S. Yue:** None. **Y. Yang:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.10/JJJ57

Topic: I.04. Physiological Methods

Support: NIH Grant DC005259
NIH Grant U01NS099691
Korea Institute of Science and Technology (KIST) grant 2E26190
Korea Institute of Science and Technology (KIST) grant 2E26170

Title: Monitoring voltage fluctuations of intracellular membranes

Authors: *M. SEPEHRI RAD[1], L. B . COHEN[1,2], B. J. BAKER[1,3]
[1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Yale Univ., New Haven, CT; [3]Dept. of Neuroscience, Korea Univ. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: In eukaryotic cells, the endoplasmic reticulum (ER) is the largest continuous membrane-enclosed network which surrounds a single lumen. Using a new genetically encoded voltage indicator (GEVI (named Aahn)), we applied the patch clamp technique to cultured HEK293 cells and neurons and found that there is a very fast electrical interaction between the plasma membrane and internal membrane(s). This discovery suggests a novel mechanism for interaction between the external membrane and internal membranes as well as mechanisms for interactions between the various internal membranes. The ER may transfer electrical signals between the plasma membrane and other internal organelles. The internal membrane optical signal is reversed in polarity but has a time course similar to that of the plasma membrane signal.

The optical signal of the GEVI in the plasma membrane is consistent from trial to trial. However, the internal signal decreases in size with repeated trials suggesting that the electrical coupling is degrading and/or the resistance of the internal membrane is decaying. Recently, we have tested the second generation of Aahn which appears to give only an internal signal.
This work was supported by the World Class Institute (WCI) Program of the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology of Korea (MEST) (NRF Grant Number: WCI 2009-003), KIST Institutional Program (Project No. 2E24310) and U.S. NIH grants DC005259 and NS099691

Disclosures: M. Sepehri Rad: None. **L. B . Cohen:** None. **B. J. Baker:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.11/JJJ58

Topic: I.04. Physiological Methods

Support: NIH Grant U01NS099691
KIST Grant 2E26190
KIST Grant 2E26170

Title: A red shifted GEVI that can resolve population signals in slice

Authors: *B. KANG[1,3], B. YI[1,3], S. LEE[2,4], B. J. BAKER[5,3]
[2]Ctr. for Functional Connectomics, [1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [3]Bio-Medical Sci. and Technol., UST, Daejeon, Korea, Republic of; [4]Dept. of Trans-Disciplinary Studies, Seoul Natl. Univ., Suwon, Korea, Republic of; [5]KIST Korea Inst. of Sci. & Tech., Seoul, Korea, Republic of

Abstract: A genetically encoded voltage indicator (GEVI) with bright emission in a red shifted spectra was developed by modifying the combination of Bongwoori voltage-sensing domain (VSD) and the red fluorescent protein (FP) dTomato. Dimerization of the FP has been shown to be critical in the mechanism of the voltage-dependent optical signal which led to the use of the very bright FP dTomato. Improvements were made by manipulating charges in the dimer interface between the red FPs and altering the linker between the VSD and FP. The resulting GEVI, called Ilmol (Korean for sunset), shows that directed mutagenesis from a mechanistic approach can successfully create probes capable of resolving action potentials in neurons and population recordings from slice.

Disclosures: B. Kang: None. **B. Yi:** None. **S. Lee:** None. **B.J. Baker:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.12/JJJ59

Topic: I.04. Physiological Methods

Support: NIH Grant U01NS099691
KIST grant 2E27850
KIST grant 2E27880
KNRF-2013H1A2A1033344

Title: The empirical nature of trafficking motifs on genetically encoded voltage indicators

Authors: *S. LEE[1,2], B. KANG[1,3], M. KIM[1], Y.-K. SONG[2,4], B. J. BAKER[1,3]
[1]Ctr. for Functional Connectomics, Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Dept. of Transdisciplinary Studies, Seoul Natl. Univ., Suwon, Korea, Republic of; [3]Div. of Bio-Medical Sci. and Technology, KIST Sch., Korea Univ. of Sci. and Technol. (UST), Seoul, Korea, Republic of; [4]Advanced Inst. of Convergence Technol., Suwon, Korea, Republic of

Abstract: Genetically encoded voltage indicators (GEVIs) convert voltage change into a fluorescence signal. GEVIs have improved, showing promising results in characterizing mammalian neuronal circuit. We recently developed a GEVI, Bongwoori-R3, that is optimized for visualizing action potential spikes in neurons. To optimize its expression in transmembrane regions thereby improving the signal-to-noise ratio, we introduced Golgi-to-plasma membrane trafficking and ER export signals. The signal sequences were introduced separately or in combination to ascertain effects on Bongwoori-R3 membrane expression. The ER export signal increased the ΔF/F but made the voltage-dependent optical signal slower. Placing spacers in between Bongwoori-R3 and the ER signal sequence alleviated this effect while keeping the improved ΔF/F size. A novel strategy to only activate the GEVI molecules in certain area was also investigated using photoactivation. We developed a photoactivatable Bongwoori-R3. After the photoactivation, this variant successfully showed voltage-dependent fluorescence signal from a mammalian cell type. In this presentation, we will also discuss strategies that we adopted and newly introduced to expand applicability of GEVIs.

Disclosures: S. Lee: None. **B. Kang:** None. **M. Kim:** None. **Y. Song:** None. **B.J. Baker:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.13/JJJ60

Topic: I.04. Physiological Methods

Support: ERC Grant #677683
ERC Grant #692943
NIH Grant U01NS094190

Title: Multifunctional tapered optical fibers for optical excitation and electrical extracellular recording using direct laser writing and two-photon lithography

Authors: *A. BALENA[1,2], A. RIZZO[1,2], E. D. LEMMA[1,2], F. PISANO[1], M. PISANELLO[1], L. SILEO[1], M. DE VITTORIO[1,2], F. PISANELLO[1]
[1]Ctr. for Biomolecular Nanotechnologies, Inst. Italiano di Tecnologia, Arnesano, Italy; [2]Ingegneria dell'Innovazione, Univ. del Salento, Lecce, Italy

Abstract: Tapered optical fibers (TF) are a versatile tool for spatially selective activation or inactivation [1] of genetically defined set of neurons at depth [2]. TFs are based on multimodal optical fibers (core size 50 - 200 µm) and a sub-µm tip for smooth insertion into the brain [2-4]. Light delivery can be confined to small apertures along a metal-coated taper by acting on the light coupling angle into the fiber. We propose a system that combines Direct Laser Writing (DLW) and 3D Two Photon Litography (TPL) to fabricate a single integrated probe capable of both optical stimulation and electrical extracellular recording. Our DLW-TPL system consists in two parallel paths that exploit an ultraviolet and an infrared laser focused on TF surface (Fig.1a). The TF is connected to a four-axis piezoelectric stage (Fig.1b) by a custom fiber holder, allowing for translation and rotation around the TF axis. The system is controlled with custom LabView software. The DLW path ablates the metal coating to obtain optical apertures all along and around the TFs [5] (Fig.1c-d). The TPL path allows for the implementation of positive photoresist patterning techniques for the realization of µ-electrodes by subsequent metal deposition and lift-off steps (Fig.1e-g). Our system exploits the advantages of TPL in terms of 3D sub-micrometer pattering on the highly non-planar surface of the fiber. Potentially, this technique can be used to fabricate µ-electrodes and mm-long conductive tracks of different size and shape. We view the proposed method as a fast and powerful technique to fabricate multifunctional neural interfaces for optogenetic applications with customized light delivery geometries and extra-cellular recording from multiple sites.
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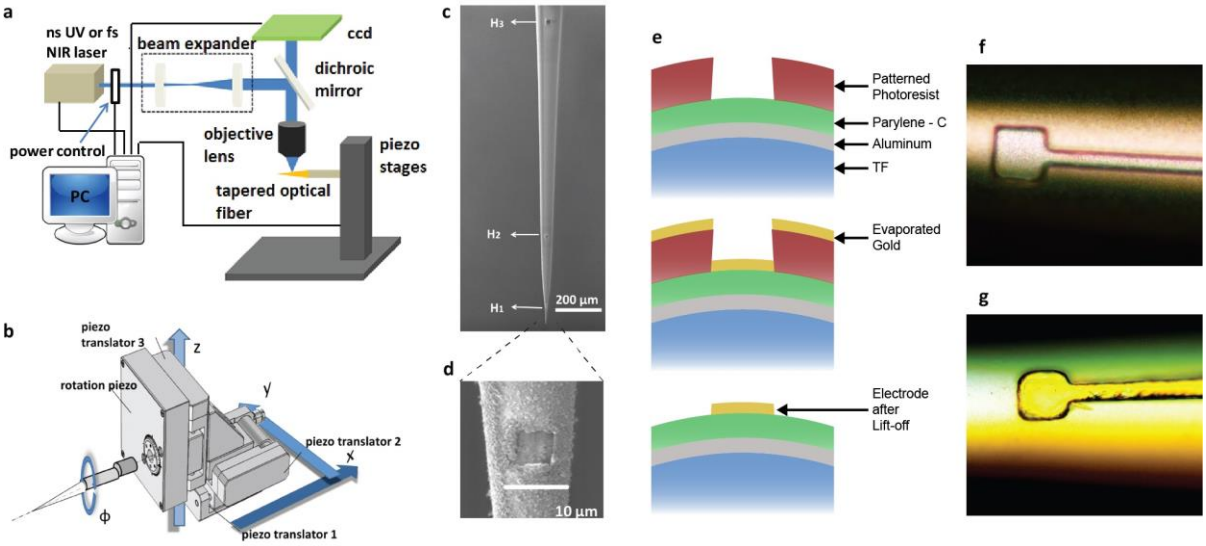


Disclosures: A. Balena: None. **A. Rizzo:** None. **E.D. Lemma:** None. **F. Pisano:** None. **M. Pisanello:** None. **L. Sileo:** None. **M. De Vittorio:** None. **F. Pisanello:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.14/JJJ61

Topic: I.04. Physiological Methods

Support: A*STAR 1334k00083 to Y.T.C
IBS-R007-A1 to X. L. and Y.T.C.
MOE2014-T2-2-071 to H.S.J.
NMRC/CBRG/0075/2014 to H.S.J.
Duke-NUS Signature Research Program Block Grant to H.S.J.
Duke-NUS-KPFA/2016/0007 to M.F.

Title: CDr20, a novel microglia specific probe for *in vivo* imaging

Authors: *M. FUKUDA[1], B. KIM[2], J. LEE[2,3,4], D. SU[2], S. SANU[2], A. T. T. KHOO[1], T. KWON[5], X. LIEU[4,6], X. LIU[7], S. CHOI[8], D. S. Y. WAN[2], J.-S. KIM[9], Y.-T. CHANG[2,4,6], H. S. JE[1,10]
[1]Program in Neurosci. and Behavioral Disorders, Duke-Nus Grad. Med. Sch., Singapore,

Singapore; [2]Lab. of Bioimaging Probe Develop., Singapore Bioimaging Consortium, Singapore, Singapore; [3]New Drug Develop. Center,, Daegu-Gyeongbuk Med. Innovation Fndn., Daegu, Korea, Republic of; [4]Dept. of Chem., Pohang Univ. of Sci. and Technol., Pohang, Korea, Republic of; [5]Dept. of Biomed. Engineering, Sch. of Life Sci., Ulsan Natl. Inst. of Sci. and Technol., Ulsan, Korea, Republic of; [6]Ctr. for Self-assembly and Complexity, Inst. for Basic Sci. (IBS), Pohang, Korea, Republic of; [7]Singapore Univ. of Technol. and Design, Singapore, Singapore; [8]Dept. of Chem., Seoul Natl. Univ., Seoul, Korea, Republic of; [9]Ctr. for Genome Engin., Inst. for Basic Sci., Daejeon, Korea, Republic of; [10]Dept. of Physiol., Yong Loo Lin Sch. of Medicine, Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Microglia are central nervous system (CNS)-resident macrophages that regulate and maintain CNS homeostasis during development and in healthy and disease states. The observation of microglia is predominantly restricted to either histopathological techniques utilizing post-mortem CNS tissues or fluorescent imaging using knock-in or transgenic mouse lines that express fluorescent proteins in microglia lineages. Therefore, efforts have been dedicated to generating or identifying biomolecules or small chemical probes that target microglia population *in situ* and *in vivo*. Through a thorough structure-activity relationships study, we developed a microglia-specific probe, CDr20, which can be applied both to *in vitro* and *in vivo* imaging. CDr20 selectively stained microglia in both cultured cells and in the rodents' brains. We confirmed that intravenously delivered CDr20 labeled cortical microglia if and only if the blood brain barrier was compromised using LPS injected animals, mild ischemia and Alzheimer's disease model animals. Through a genome-scale CRISPR-Cas9 screening, we found that Ugt1a7c turns on the fluorescence of CDr20 by enzymatic glucuronidation reaction in microglia. Since the target enzyme of Ugt1a7c was the only type of Ugt genes highly enriched in microglia, this research will lead an interest its functional role in the brain, and Ugt1a7c can be used as a novel marker of microglia.

Disclosures: M. Fukuda: None. **B. Kim:** None. **J. Lee:** None. **D. Su:** None. **S. Sanu:** None. **A.T.T. Khoo:** None. **T. Kwon:** None. **X. Lieu:** None. **X. Liu:** None. **S. Choi:** None. **D.S.Y. Wan:** None. **J. Kim:** None. **Y. Chang:** None. **H.S. Je:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.15/JJJ62

Topic: I.04. Physiological Methods

Support: JSPS KAKENHI Grant Number JP17H02088
Grant by Foundation for Promotion of Material Science and Technology of Japan

Title: Serotonin imaging using serotonin-imprinted fluorescent polymer nanoparticles as a probe

Authors: *R. MORI, K. UMETA, Y. KATSUMATA, S. ISHIDA, Y. YOSHIMI
Shibaura Inst. of Technol., Koto-ku, Toyosu, Japan

Abstract: A Molecularly Imprinted Polymer (MIP) is a polymer that has been processed using the molecular imprinting technique which leaves cavities in polymer matrix with affinity to a chosen "template" molecule. Thus, we attempt to develop a probe tracing neurotransmitter using a fluorescent nanoparticle of MIP (fMIP-NP) of the target neurotransmitter as a template. In this study, serotonin was chosen as the target neurotransmitter. Serotonin was immobilized on glass beads via silane coupler. The beads were fluidized in a solution of a functional monomer which has affinity with serotonin, a crosslinking monomer, a fluorescent monomer and a radical polymerization under UV irradiation. The synthesized copolymer was removed from the beads by washing with acetonitrile. After evaporation of the acetonitrile, the copolymer was dispersed as fMIP-NP in 0.1 M phosphate buffered saline at pH 7.4. The radius and fluorescent intensity of fMIP-NP were sensitive to serotonin but were insensitive to L-tryptophan (The results will be presented in this meeting separately). A 0.1 mM serotonin solution was injected into the fMIP-NP dispersion under observation with a fluorescent imaging system (MiCAM02, Brainvision Inc.). The fluorescent intensity was increased by 2.6% with a time lag of several-ten milliseconds. The result indicates that the fMIP-NP can work as a rapidly responsive probe. A cerebral ganglion of Aplysia was stained by immersion in an artificial sea water dispersed with the fMIP-NP for 24 hours. The ganglion was observed by the fluorescent imaging system. As a result, only one neuron in the vicinity of the serotonergic neurons (MCC) indicated spiked change of 0.05 % in the fluorescent intensity an interval of 50 ms. Those results indicate that the fMIP-NP of serotonin is feasible for detection of serotonin secreted in living nervous system. Molecular imprinting technology can target many kinds of chemicals, then fMIP-NP would contribute to elucidate the roles of each neurotransmitters in nervous systems.

Disclosures: R. Mori: None. **K. Umeta:** None. **Y. Katsumata:** None. **S. Ishida:** None. **Y. Yoshimi:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.16/JJJ63

Topic: I.04. Physiological Methods

Support: NSF NeuroNex 1707359
The Robert and Janice McNair Foundation
The John S. Dunn Foundation

Title: Development, characterization, and deployment of a new generation of genetically encoded voltage indicators

Authors: *F. ST-PIERRE[1,2], Z. LIU[2], Y. GOU[1], S. GUAN[1], X. LU[2], J. LEE[2], J. YANG[2], P. SUZUKI[2], S. CAO[2], A. TOLIAS[1]
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Rice Univ., Houston, TX

Abstract: A longstanding goal in neuroscience is to understand how spatiotemporal patterns of neuronal electrical activity underlie brain function, from sensory representations to decision making. An emerging technology for monitoring electrical dynamics is voltage imaging using Genetically Encoded Voltage Indicators (GEVIs) — light-emitting protein indicators whose brightness directly reports voltage. GEVIs are promising tools for monitoring voltage dynamics at high spatiotemporal resolution in genetically defined cell types *in vivo*. Indicator performance has steadily progressed since GEVIs were first reported; they have also been deployed in multiple animal systems. For example, we have recently demonstrated two-photon voltage imaging in organotypic slice cultures and in *Drosophila* with millisecond-timescale precision, subcellular resolution, and the ability to simultaneously monitor spatially-segregated locations. However, despite significant progress made so far by the GEVI community, the performance of current voltage indicators is usually insufficient for robust single-trial two-photon imaging of voltage dynamics of many individual neurons in behaving rodents. As a result, GEVIs have yet to be broadly adopted. The mechanisms of voltage indicators are insufficiently understood to enable purely rational engineering of new GEVIs with predictable outcomes, motivating the evaluation of many candidates to identify improved variants. As screening by patch-clamp electrophysiology can only evaluate fewer than ~10 new candidates per day, we are developing a pipeline for high-throughput screening of GEVI libraries, followed by detailed characterization of the most promising candidates. Here, we will present our ongoing efforts to develop improved methods for screening variants of the Accelerated Sensor of Action Potential (ASAP) voltage indicator family. We also present promising candidates identified during our screens. We anticipate that these efforts will ultimately produce high-performing indicators of broad utility for imaging spontaneous voltage dynamics in the brains of behaving animals.

Disclosures: F. St-Pierre: None. **Z. Liu:** None. **Y. Gou:** None. **S. Guan:** None. **X. Lu:** None. **J. Lee:** None. **J. Yang:** None. **P. Suzuki:** None. **S. Cao:** None. **A. Tolias:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.17/JJJ64

Topic: I.04. Physiological Methods

Support: NIH NS083875
NIH UO1NS090565
NIH UO1NS103517

NIH DC005259
NIH DC016133
NIH UO1 NS099691
KIST 2E267190

Title: *In vivo* imaging of odor-evoked electrical activity in targeted cell populations in the olfactory bulb of transgenic mice expressing the GEVI ArcLight

Authors: *J. PLATISA[1,2], L. MADISEN[3], H. ZENG[3], L. B. COHEN[2,4], V. A. PIERIBONE[1,2], D. A. STORACE[2]
[1]The John B Pierce Lab., New Haven, CT; [2]Yale Univ., New Haven, CT; [3]Allen Inst. for Brain Sci., Seattle, WA; [4]KIST Ctr. for Functional Connectomics, Seoul, Korea, Republic of

Abstract: Genetically encoded voltage indicators (GEVIs) allow for optical recordings of membrane potential from genetically defined cell populations. Recently developed GEVIs have dramatically improved signal-to-noise ratios that increase the fidelity of measurements of neuronal activity *in vitro* and *in vivo*. However, there is limited *in vivo* data from transgenic mice expressing GEVIs in targeted cell populations. Here we used Cre/tTA dependent expression of the GEVI ArcLight to generate knock-in transgenic mice with different expression patterns in the olfactory bulb. Odor-evoked optical signals were detectable in single trials using both widefield epifluorescence and 2-photon imaging. Our results demonstrate that the ArcLight transgenic line is a flexible genetic tool that can be used to record neuronal electrical activity of a variety of cell types with a signal-to-noise that is comparable to previous reports using viral transduction.

Disclosures: J. Platisa: None. **L. Madisen:** None. **H. Zeng:** None. **L.B. Cohen:** None. **V.A. Pieribone:** None. **D.A. Storace:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.18/JJJ65

Topic: I.04. Physiological Methods

Support: NIH 1R21 EY027562
NIH R01 NS101106
NIH T32 GM008275

Title: Biophysical approaches for designing voltage-sensing probes

Authors: *M. J. IWANICKI, J. A. MANCINI, S. MUKHERJEE, C. C. MOSER, B. Y. CHOW, B. M. DISCHER
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Neurons transmit information to other neurons by utilizing voltage signaling, and by imaging these signals on faster timescales, a greater understanding of interneuronal communication can be achieved. Organic voltage-sensing probes were first developed to measure voltage signaling in neurons. While many organic probes have been developed to detect signals with fast temporal resolution, they cannot be targeted to a specific cell or membrane. Genetically-encoded voltage indicators (GEVIs), which typically includes a voltage-sensing domain of a natural protein, were engineered to improve genetic targetability. However, GEVIs tend to be slower, dimmer, and not as sensitive as organic voltage-sensing probes. Here, we present our progress on the development and characterization of *de novo* designed GEVIs based on artificial 4-α-helical bundle proteins, called maquettes. Maquettes have been designed to be able to attach various natural cofactors and can either be water-soluble or transmembrane constructs. We are developing two classes of maquette GEVIs. The first class involves covalently attaching a fluorescent cofactor to the core of the maquette. We are using a direction evolution approach in order to improve its fluorescent signal and quantum yield. The second class is a fusion construct of a maquette and a fluorescent protein, whose fluorescence can be modulated by the redox state of heme. Energy transfer between the fluorescent protein and the maquette has been demonstrated upon heme reduction. Our current GEVI prototypes have been expressed in *E. coli* and characterized *in vitro*. The modular nature of these probes allows us to optimize the intensity and to tune their speed to be within the desirable range. We are also optimizing the sequences for plasma membrane trafficking in hippocampal neurons to validate the *in vitro* biophysical approach in mammalian cells.

Disclosures: M.J. Iwanicki: None. **J.A. Mancini:** None. **S. Mukherjee:** None. **C.C. Moser:** None. **B.Y. Chow:** None. **B.M. Discher:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.19/JJJ66

Topic: I.04. Physiological Methods

Support: Howard Hughes Medical Institute

Title: Engineering next generation voltage indicators using high-throughput screening

Authors: *D. S. KIM[1], B. J. ARTHUR[1], A. S. ABDELFATTAH[1], G. CAO[1], I. KOLB[1], A. SINGH[1], O. NOVAK[2], Y. SUN[1], J. P. HASSEMAN[1], G. TSEGAYE[1], A. K. TSANG[1], D. N. MERRYWEATHER[1], V. JAYARAMAN[1], L. D. LAVIS[1], E. R. SCHREITER[1], L. L. LOOGER[1], K. SVOBODA[1]
[1]Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA; [2]Inst. of Exptl. Med., Acad. of Sci. of the Czech Republic, Prague, Czech Republic

Abstract: Genetically encoded voltage indicators (GEVIs) can be used to image neuronal activity *in vivo*. GEVIs detect neuronal membrane voltage changes, including action potentials and subthreshold activity. Moreover, the activity of distinct neuron subtypes can be followed by expressing GEVIs using cell type-specific promoters. However, current GEVIs exhibit relatively low sensitivity, inefficient membrane expression, and poor photostability, which limit their utility for *in vivo* imaging of neuronal populations. To improve GEVI performance, we created libraries of novel variants by structure-guided or unbiased mutagenesis and assayed activity using high-throughput screening. We used tissue culture cells for screening that can be induced to spike from a resting membrane potential by electrical field stimulation. These cells stably express voltage-gated sodium and inwardly rectifying potassium channels and are readily transduced with GEVI constructs. This enables a throughput of ~10^4 constructs screened per year in replicate. Fluorescence imaging was performed on a motorized microscope in an automated manner. Promising constructs were further tested in cultured neurons in response to action potentials or voltage steps. In order to improve sensor membrane expression, the membrane trafficking of the best variants was quantified in relation to the response amplitude by epitope labeling of surface versus internal membrane-expressed sensor proteins. We report on the higher sensitivity, faster kinetics, and shifted voltage range of new variants of the existing GEVIs: ArcLight, MARINA, ASAP, and the novel chemigenetic GEVI, Voltron. These next generation GEVIs will be useful for the correlation of neuronal activity *in vivo* with animal behavior.

Disclosures: D.S. Kim: None. **B.J. Arthur:** None. **A.S. Abdelfattah:** None. **G. Cao:** None. **I. Kolb:** None. **A. Singh:** None. **O. Novak:** None. **Y. Sun:** None. **J.P. Hasseman:** None. **G. Tsegaye:** None. **A.K. Tsang:** None. **D.N. Merryweather:** None. **V. Jayaraman:** None. **L.D. Lavis:** None. **E.R. Schreiter:** None. **L.L. Looger:** None. **K. Svoboda:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.20/JJJ67

Topic: I.04. Physiological Methods

Support: NSF Brain EAGER 1611090

Title: A nanophotonic multi-beam probe for simultaneous deep brain optogenetic stimulation and electrical recording *in vivo*

Authors: *Q. LI[1], A. MOHANTY[2], S. P. ROBERTS[3], M. A. TADAYON[2], M. LIPSON[4], A. KEPECS[1]
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Dept. of Electrical Engin., [3]Dept. of

Electrical Engineering,, Columbia Univ., New York, NY; [4]Columbia Univ., Dept. of Electrical Engin., New York, NY

Abstract: Optogenetics has revolutionized the investigation of neural network function. In many experiments, especially those coupled with electrophysiology, a single optical fiber is used to flood a large area of the brain with light, limiting the ability to activate neurons with high spatial resolution in vivo. Here we develop an active nanophotonic multi-beam probe integrated with recording electrodes which enables deep brain neural activation and extracellular spike recording with high fidelity in space and time. The active silicon photonics technology overcomes the limited reconfigurability of traditional optics and results in an unprecedented amount of optical control, matching the scale and resolution currently achieved by silicon probes for electrophysiological recordings. The demonstrated probe employed a 1x8 multipoint-emitting nanophotonic switch leading to an array of grating emitters (emitter size: 20 x 20 μm, 125 μm inter-beam distance) and platinum recording electrodes (size: 30 μm diameter) within 20 μm of each emitter. The nanophotonic switching electronics and the recording electrodes were co-fabricated on the same metal layer and insulated using SU8. Using an optimized nanophotonic architecture, we were able to achieve ON/OFF switch ratios of greater than 50:1. In this work, we injected AAV-EF1a-DIO-ChETA-eYFP virus (ChETA, a channelrhodopsin-2 variant which enables ultrafast optogenetic control) into the visual cortex of Gad2-IRES-Cre transgenic knock-in mice, and implanted the 8-beam nanophotonic probe into the visual cortex in anesthetized mice. By applying voltages to the nanophotonic switch network, we routed 473 nm blue light to 8 output grating light emitters and independently activated individual ChETA-expressing Gad2 interneurons across layer 2-6 of visual cortex with customer programmed patterns. In conclusion, we show that the nanophotonic platform can be successfully integrated with high-density electrical recording sites to create or edit complex neural activity. Scaling it up to a larger number of beams (e.g.128) is expected to be straightforward since these devices are defined lithographically, enabling high spatiotemporal resolution optical stimulation in deep brain regions.

Disclosures: Q. Li: None. **A. Mohanty:** None. **S.P. Roberts:** None. **M.A. Tadayon:** None. **M. Lipson:** None. **A. Kepecs:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.21/JJJ68

Topic: I.04. Physiological Methods

Support: Grant/Other Support: NIH Grant U01NS099691
Grant/Other Support: KIST Grant 2E26190

Grant/Other Support: KIST Grant 2E26170

Title: Engineering of voltage sensing domains for optical resolution of differing neuronal activities

Authors: *A.-R. JUNG[1], J. CHOI[2], E. HWANG[2], B. J. BAKER[1]
[1]KIST Korea Inst. of Sci. & Tech., Seoul, Korea, Republic of; [2]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: To optically resolve different types of neuronal activities, we have developed several types of genetically encoded voltage sensing indicators (GEVIs). To develop GEVIs that can only resolve hyperpolarization (inhibition), we manipulated movement of the voltage-sensing domain with tryptophan residues. Our data suggest that several positions of Tryptophan inhibit the movement of S4 during membrane depolarization. To make stronger and a better for the signal to noise ratio inhibition probe, we inserted several Tryptophan's into the voltage sensing domains. Insertion of a tryptophan residue in the S1 or/and S4 α-helix dramatically reduced the optical signal for depolarization while maintaining the fluorescent response during hyperpolarization of the plasma membrane. As a result, the optical activities of some probes are biased towards optically resolving neuronal inhibition.

Disclosures: A. Jung: None. **J. Choi:** None. **E. Hwang:** None. **B.J. Baker:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.22/JJJ69

Topic: I.04. Physiological Methods

Support: National Basic Research Program of China Grant 2015CB856402
NIH brain initiative grant NS103558

Title: Development and application of a novel genetically-encoded serotonin sensor

Authors: *J. WAN[1,2,3], M. JING[2,3,4], J. FENG[2,3,4], J. ZOU[5,6], J. ZENG[2,3,4], C. WEI[7], H. WANG[1,2,3], M. LUO[7,8], S. TANG[1], Y. LI[1,2,3,4]
[1]Sch. of Life Sci., Peking Univ., Beijing, China; [2]PKU-IDG/McGovern Inst. for Brain Res., Beijing, China; [3]State Key Lab. of Membrane Biol., Peking Univ. Sch. of Life Sci., Beijing, China; [4]Peking-Tsinghua Ctr. for Life Sci., Beijing, China; [5]Dept. of Biol. Sci., USC, Los Angeles, CA; [6]Life Sci. Honors' Program, China Agr. Univ., Beijing, China; [7]Natl. Inst. of Biol. Sci., Beijing, China; [8]Sch. of Life Sciences, Tsinghua Univ., Beijing, China

Abstract: Serotonin (5-HT) is an important monoamine neuromodulator in the nervous system, critical for learning, appetite control, sleep regulation, and many other cognitive functions. Malfunctions of 5-HT regulation are associated with several neurological diseases including depression, addiction and compulsivity. Despite its importance, deciphering the physiological function and regulation of 5-HT are currently hindered by the lack of non-invasive methods with good spatiotemporal resolution in tracking 5-HT dynamics *in vivo*. Here we successfully developed a novel genetically-encoded fluorescent 5-HT sensor ($GRAB_{5\text{-}HT}$), through coupling of a conformationally sensitive circular-permutated EGFP with an endogenous 5-HT sensing GPCR. We show that $GRAB_{5\text{-}HT}$ enables *in vivo* cell-specific monitoring of odor-evoked 5-HT secretion in *Drosophila*, as well as tracking dynamic changes of dorsal raphe 5-HT levels during reward conditioning in freely moving mice. Finally, $GRAB_{5\text{-}HT}$ could be long-term expressed, up to 6 months, in non-human primates without noticeable toxicity, and is capable of reporting specific changes of 5-HT concentration under two-photon imaging condition. These data together demonstrate $GRAB_{5\text{-}HT}$ is a useful and broad applicable probe for understanding the physiological and pathophysiological function of 5-HT in diverse model organisms.

Disclosures: J. Wan: None. **M. Jing:** None. **J. Feng:** None. **J. Zou:** None. **J. Zeng:** None. **C. Wei:** None. **H. Wang:** None. **M. Luo:** None. **S. Tang:** None. **Y. Li:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.23/JJJ70

Topic: I.04. Physiological Methods

Support: NIH brain initiative grant NS103558
National Basic Research Program of China, 973 Program 2015CB856402)
General Program of National Natural Science Foundation of China 31671118 and 31371442

Title: A specific genetically-encoded sensor for norepinephrine

Authors: *J. FENG[1,2,3], M. JING[1,2,3], C. ZHANG[4], H. WANG[2,3], Y. ZHANG[3], H. LI[5], J. ZHU[6], J. DU[4], Y. LI[1,2,3]
[1]Ctr. for Life Sci., Peking Univ., Beijing, China; [2]PKU-IDG/McGovern Inst. for Brain Res., Beijing, China; [3]State Key Lab. of Membrane Biol., Peking Univ. Sch. of Life Sci., Beijing, China; [4]Inst. of Neurosci., Chinese Acad. of Sci., Shanghai, China; [5]Wuhan Natl. Lab. for Optoelectronics, Wuhan, China; [6]Sch. of Med., Univ. of Virginia, Charlottesville, VA

Abstract: Norepinephrine (NE) and epinephrine (Epi), important biogenic monoamine neurotransmitters, are involved in many crucial physiological processes in diverse organs.

However, the precise function and regulation of adrenergic and noradrenergic transmission in the majority of tissues remains poorly understood due partly to the limitations of the available techniques for monitoring their release. Here we developed a G-protein-coupled Receptor Activation-based Epi/NE sensor ($GRAB_{NE}$). $GRAB_{NE}$ sensor responds to exogenous NE and Epi with $\Delta F/F \sim 200\%$ and no apparent ectopic activation of downstream G protein and β-Arrestin pathways. $GRAB_{NE}$ preserves the ligand binding pocket of endogenous adrenergic receptors and has an EC_{50} to NE ~1 μM. $GRAB_{NE}$ sensor specifically detects both exogenous and endogenous NE in brain slices under 2-photon microscopy. *In-vivo* application of $GRAB_{NE}$ sensor in awake zebrafish and behaving mice unravel their capacity and robustness in specifically revealing endogenous NE dynamics. Thus, $GRAB_{NE}$ sensor provides a new genetically-encoded tool for dynamically monitoring adrenergic and noradrenergic transmission during physiological and pathological processes.

Disclosures: J. Feng: None. **M. Jing:** None. **C. Zhang:** None. **H. Wang:** None. **Y. Zhang:** None. **H. Li:** None. **J. Zhu:** None. **J. Du:** None. **Y. Li:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.24/LLL1

Topic: I.04. Physiological Methods

Support: National Basic Research Program of China 2015CB856402
The General Program of National Natural Science Foundation of China 31671118
The General Program of National Natural Science Foundation of China 31371442

Title: a family of genetically-encoded fluorescent acetylcholine indicators

Authors: *M. JING[1], P. ZHANG[3], G. WANG[4], J. FENG, Mrs[2], Y. LI, miss[2], L. MESIK[5], L. I. ZHANG[5], M. LUO[6], Y. SONG, mrs[2], H. LI, mr[7], J. ZHU[8], M. XU[9], Y. LI[2]
[1]Sch. of Life Sci., [2]Peking Univ., Beijing, China; [3]Pharmacol., [4]Univ. of Virginia, Charlottesville, VA; [5]USC, Los Angeles, CA; [6]Natl. Inst. of Biol. Sci., Beijing, China; [7]Wuhan Natl. Lab. for Optoelectronics, Wuhan, China; [8]Dept Pharmacol, Univ. VA Sch. Med., Charlottesvle, VA; [9]Inst. of Neuroscience, Chinese Acad. of Scie, Shanghai City, China

Abstract: Acetylcholine (ACh) regulates a diverse array of physiological processes throughout the body, yet cholinergic transmission in the majority of tissues/organs remains poorly understood due primarily to the limitations of available ACh-monitoring techniques. By tapping into the native ACh sensing GPCRs, we here developed a family of G-protein-coupled receptor activation-based ACh sensors (GACh), with high sensitivity, specificity, signal-to-noise ratio, kinetics and photostability suitable for monitoring ACh signals in multiple preparations

including cultured cells and acute slices *in vitro* and living *Drosophila* and mice *in vivo*. Taking advantage of the novel GACh sensors, we successfully tracked the dynamics of endogenous ACh in real-time, revealing presynaptic regulation as well as firing-pattern dependent of cholinergic transmission. Furthermore, we recently developed newer GACh sensors with even larger dynamic range, offering improved probes to resolve physiological ACh levels. In sum, GACh sensors provide a convenient, broadly applicable tool for monitoring cholinergic transmission underlying diverse biological processes.

Disclosures: M. Jing: None. **P. Zhang:** None. **G. Wang:** None. **J. feng:** None. **Y. li:** None. **L. Mesik:** None. **L.I. Zhang:** None. **M. Luo:** None. **Y. song:** None. **H. li:** None. **J. Zhu:** None. **M. Xu:** None. **Y. Li:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.25/LLL2

Topic: I.04. Physiological Methods

Support: National Basic Research Program of China (973 Program; grant 2015CB856402)
General Program of National Natural Science Foundation of China (project 31671118 and project 31371442)
Junior Thousand Talents Program of China to Y. L.

Title: A toolbox of genetically-encoded fluorescent sensors for monitoring purinergic neurotransmitters

Authors: *Y. LI[1,2,3,4], H. WANG[3,4], Z. WU[3,4], H. WU[5], L. DONG[2,4], K. HE[5], M. XU[6,7]
[1]Peking Univ., Beijing, China; [2]Peking-Tsinghua Ctr. for Life Sci., Beijing, China; [3]State Key Lab. of Membrane Biol., Peking Univ. Sch. of Life Sci., Beijing, China; [4]PKU-IDG/McGovern Inst. for Brain Res., Beijing, China; [5]Sch. of Life Sci. Tsinghua Univ., Beijing, China; [6]Inst. of Neuroscience, Chinese Acad. of Scie, Shanghai City, China; [7]Chinese Acad. of Sci. Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China

Abstract: Purinergic molecules, e.g. ATP, ADP, AMP and adenosine, are playing important roles in a plethora of physiological processes, including sleep-wake control, learning and memory, as well as cell proliferation, cardiovascular activity and immune response. Malfunction of purinergic signaling is implicated in diseases such as pain, migraine, epileptic seizures and drug addiction. A major obstacle to decipher physiological and pathophysiological function of purinergic transmission is the lack of direct, sensitive, and non-invasive method to monitor and discern structural similar purinergic neurotransmitters, ideally with high spatial and temporal resolution *in vivo*. Here by tapping into naturally evolved adenosine receptors and purinergic

P2Y receptors, we developed a toolbox of distinct genetically-encoded fluorescent sensors, with unique molecular specificity for adenosine, ADP, ATP and UTP. These novel fluorescent sensors utilize metabotropic GPCR receptors as ligand sensing modules and circular-permutated GFPs as optical outputs. They have good membrane localization and exhibit robust fluorescence increase (~ 100% dF/F or more) upon cognate ligand application when expressed in cultured HEK239T cells. In addition, these sensors have nano- to micro-molar affinities to distinct purinergic molecules, very similar to native adenosine and P2Y receptors. Using these sensors, we successfully monitored neuronal- or glial- derived extracellular adenosine levels upon electric or high KCl stimulation. In addition, using fiber photometry, we are able to observe sleep-awake relevant changes of adenosine levels in mice *in vivo*. The development of these genetically-encoded purinergic neurotransmitter sensors provides a critical tool for better understanding of purinergic signaling in physiological and pathological processes with molecular specificity.

Disclosures: Y. Li: None. **H. Wang:** None. **Z. Wu:** None. **H. Wu:** None. **L. Dong:** None. **K. He:** None. **M. Xu:** None.

Poster

699. Physiological Methods: Optical Methodology: Probes

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 699.26/LLL3

Topic: I.04. Physiological Methods

Support: National Basic Research Program of China (973 Program; grant 2015CB856402)
General Program of National Natural Science Foundation of China (project 31671118 and project 31371442)
NIH brain initiative grant NS103558
Junior Thousand Talents Program of China to Y.Li and to S.Zhang
Ministry of Science and Technology of the People's Republic of China (2017YFA0505703) to M.Xu

Title: A genetically-encoded fluorescent sensor enables rapid and specific detection of dopamine in flies, fish, and mice

Authors: *J. ZENG[1,2,3,4], F. SUN[1,2,4], M. JING[1,2,3,4], J. ZHOU[5], J. FENG[1], S. F. OWEN[6], Y. LUO[1], F. LI[7], T. YAMAGUCHI[8], Z. YONG[9], Y. GAO[8], W. PENG[7], L. WANG[10], S. ZHANG[10], J. DU[7], D. LIN[8], M. XU[7], A. C. KREITZER[6], G. CUI[5], Y. LI[1,2,3,4]
[1]Peking Univ., Beijing, China; [2]State Key Lab. of Membrane Biology, Peking Univ. Sch. of Life Sci., Beijing, China; [3]Peking-Tsinghua Ctr. for Life Sci., Beijing, China; [4]PKU-IDG/McGovern Inst. for Brain Res., Beijing, China; [5]Neurobio. Lab., NIH/NIEHS, RTP, NC; [6]Gladstone Inst., San Francisco, CA; [7]Inst. of Neuroscience, CAS, Shanghai, China; [8]Smilow Neurosci. Program,

New York Univ. Sch. of Med., New York, NY; [9]China Agr. Univ., Beijing, China; [10]Shanghai Jiao Tong Univ. Sch. of Med., Shanghai, China

Abstract: Dopamine (DA) is a central monoamine neurotransmitter involved in many physiological and pathological processes. A longstanding yet largely unmet goal is to measure DA changes reliably and specifically with high spatiotemporal precision, particularly in animals executing complex behaviors. Here we report the development of novel genetically-encoded GPCR-Activation-Based-DA ($GRAB_{DA}$) sensors that enable these measurements. In response to extracellular DA rises, $GRAB_{DA}$ sensors exhibit large fluorescence increases ($\Delta F/F_0$~90%) with sub-second kinetics, nanomolar to sub-micromolar affinities, and excellent molecular specificity. Importantly, $GRAB_{DA}$ sensors can resolve a single-electrical-stimulus evoked DA release in mouse brain slices, and detect endogenous DA release in the intact brains of flies, fish, and mice. In freely-behaving mice, $GRAB_{DA}$ sensors readily report optogenetically-elicited nigrostriatal DA release and depict dynamic mesoaccumbens DA changes during Pavlovian conditioning or during sexual behaviors. Thus, $GRAB_{DA}$ sensors enable spatiotemporal precise measurements of DA dynamics in a variety of model organisms while exhibiting complex behaviors.

Disclosures: J. Zeng: None. **F. Sun:** None. **M. Jing:** None. **J. Zhou:** None. **J. Feng:** None. **S.F. Owen:** None. **Y. Luo:** None. **F. Li:** None. **T. Yamaguchi:** None. **Z. Yong:** None. **Y. Gao:** None. **W. Peng:** None. **L. Wang:** None. **S. Zhang:** None. **J. Du:** None. **D. Lin:** None. **M. Xu:** None. **A.C. Kreitzer:** None. **G. Cui:** None. **Y. Li:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.01/LLL4

Topic: I.04. Physiological Methods

Support: EU, ERC Advanced Grant “neuroXscales”, contract number 694829
EU, ERC-PoC “MwHresEP", contract number 755383
CH, Project CTI-No. 25933.2 PFLS-LS “Multi-well electrophysiology platform for high-throughput cell-based assays”

Title: Electrophysiological phenotype characterization of human iPSC-derived dopaminergic neuronal lines by means of high-resolution microelectrode array

Authors: *M. FISCELLA[1,2], N. LEARY[1], S. RONCHI[1], A. HIERLEMANN[1]
[1]ETH Zurich, Basel, Switzerland; [2]MaxWell Biosystems AG, Basel, Switzerland

Abstract: High-resolution-microelectrode-array (HD-MEA) technology enables to study neuronal dynamics at different scales, ranging from axonal physiology to network connectivity

[1]. We have used this HD-MEA technology to characterize and compare the electrical phenotypes of commercially available human dopaminergic neurons (iCell DopaNeurons, MyCell DopaNeurons A53T α-synuclein, Cellular Dynamics International, Madison, WI, US). Furthermore, we have studied the effect of human astrocytes (iCell Astrocytes, Cellular Dynamics International, Madison, WI, US) on neural-culture development. Astrocyte/neuron co-cultures showed higher signal amplitudes and higher firing rates than neural cultures without astrocytes. Adding astrocytes to neural cultures changed the whole culture morphology by promoting cell clustering. Interestingly, astrocyte/neuron co-cultures showed a lower sample-to-sample variability across multiple HD-MEA recordings compared to neural cultures without astrocytes. We compared action potential propagation velocities along axons between dopaminergic A53T α-synuclein neurons and the wild-type isogenic control cell line. We found that in both, wild-type and disease-model neurons, axonal action potential propagation velocities were lower than in rat primary cortical neurons [2]. Furthermore, we found different axonal-action-potential-velocity-development profiles of A53T α-synuclein dopaminergic neurons and the wild-type counterpart. Finally, we were able to precisely evoke action potentials in individual single human neurons by subcellular-resolution electrical stimulation. HD-MEA systems enable to access novel electrophysiological parameters of iPSC-derived neurons, which can be potentially used as biomarkers for phenotype screening and drug testing.

1. Müller et. al, Lab on a Chip, 2015
2. Bakkum et. al, Nature Communications, 2013

Disclosures: M. Fiscella: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MaxWell Biosystems AG. **N. Leary:** None. **S. Ronchi:** None. **A. Hierlemann:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.02/LLL5

Topic: I.04. Physiological Methods

Title: Evaluation of convulsant-induced firings in cultured human iPS cell-derived neurons using principal component analysis

Authors: *Y. ISHIBASHI[1], A. ODAWARA[2,4,5], A. OKAMURA[6], K. KINOSHITA[7], T. SHIRAKAWA[7,8], I. SUZUKI[3,8]
[1]Electronics, Tohoku Inst. of Technol., Sendai-Shi, Japan; [2]Tohoku Inst. of Technol., Sendai, Japan; [3]Tohoku Inst. of Technol., Sendai, Miyagi, Japan; [4]Tohoku University, AIMR, Sendai, Japan; [5]Japan Society for the Promotion of Sci., Tokyo, Japan; [6]Astellas Parma Inc., Tokyo,

Japan; [7]Astellas Pharma Inc., Tokyo, Japan; [8]Consortium for Safety Assessment using Human iPS Cells (CSAHi), Tokyo, Japan

Abstract: Human iPSC-derived neurons are expected to be applied to toxicity evaluations in nonclinical studies. One of the major toxicities of the central nervous system in clinical trials is convulsions. Multi-electrode array (MEA) systems have recently attracted attention as useful for evaluating convulsions because they can non-invasively measure the electrophysiological activities of neural networks. We have previously reported the electrophysiological responses to several convulsive compounds using MEA in cultured hiPSC-derived neurons. However, the identification of analytical parameters to detecting epileptiform activities remains an important issue. In this study, we developed a novel analytical method to quantify the periodicity of synchronized burst firings as one of the effective parameters for detecting epileptiform activities. We also identified the parameter sets that can separate the responses between convulsive drugs and negative control acetaminophen, and the responses among the several convulsants with different action mechanism using principal component analysis of 10 parameters. The parameters related to periodicity including new method developed by us were effective for the separation of convulsants and negative control. In this principal component analysis method using the identified parameter set, reproducibility was also confirmed in data of different samples. These our analysis method will be effective for detecting convulsive response and predicting mechanism of action of convulsive drugs.

Disclosures: Y. Ishibashi: 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.; Astellas Pharma Inc. **A. Odawara:** 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.; Astellas Pharma Inc. **A. Okamura:** 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.; Astellas Pharma Inc. **K. Kinoshita:** 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.; Astellas Pharma Inc. **T. Shirakawa:** 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.; Astellas Pharma Inc. **I. Suzuki:** 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.; Astellas Pharma Inc..

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.03/LLL6

Topic: I.04. Physiological Methods

Support: Volkswagen Stiftung Grant A112582
Neuratect Challenge, NC3Rs

Title: An *in vitro* 3D platform for functional and structural interrogation of neuronal circuits

Authors: B. M. MOLINA[1], P. D. JONES[2], L. JENTSCH[1], *P. CESARE[3]
[1]Neuro Microphysiological Systems, [2]Microsystems and Nanotechnology, [3]NMI, Reutlingen, Germany

Abstract: In the quest for developing new therapies for neurological disorders, researchers are still largely dependent on 2D in vitro experiments and animal models. Poorly representing the multifaceted nature of neurodegenerative processes in the human brain, these approaches have shown low predictive value in clinical studies.
To fill this gap, several public and private initiatives are focusing on the development of so called organs-on-chips. By combining advanced microfabrication and 3D cell culture technologies, these are expected to better recapitulate the physiology of the brain and capture its complexity at both structural and functional level, which may eventually lead to more relevant in vitro models of human neuronal disorders and consequently to a more efficacious drug discovery process.
However, despite the recent progresses in this field, none of the currently available technologies has the capability to directly measure electrical excitability of individual neurons synaptically connected in 3D neuronal circuits.
To address this need, our group is developing a novel phenotypic platform based on the integration of microfabrication methods, electrode arrays and microfluidics to reconstruct, record and image 3D brain circuits non-invasively in a high-throughput format.
For this purpose, mouse primary hippocampal neurons are grown embedded within hydrogel scaffolds to recreate 3D multicellular architectures inside microfabricated, pump-free bioreactors. Microelectrode arrays are then integrated into the microfluidic design and used to monitor the electrical activity of enclosed neuronal cells at different time points and in response to a range of neuroactive compounds. In parallel, morphological and 3D structural information of neurons can be collected at high-resolution by confocal microscopy following transduction with AAV particles encoding for fluorescent proteins. To meet the throughput requirements associated to pre-clinical research, up to twelve independent experiments can be carried out simultaneously on a single device having a footprint of only 49 x 49 mm. Future developments

may include integration of such technology into a format compatible with multi-well plates. Collectively, such technology has the potential to introduce a new paradigm in basic and applied neuroscience by providing a novel ground-breaking platform for investigating 3D neuronal circuits in vitro. By enabling a more physiologically relevant disease modelling, this will lead to: i) better understanding of basic neuronal mechanisms; ii) refinement of pre-clinical research methods; iii) reduction in the number of animal studies.

Disclosures: B.M. Molina: None. **P.D. Jones:** None. **L. Jentsch:** None. **P. Cesare:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.04/LLL7

Topic: I.04. Physiological Methods

Support: Astellas aspiring alliance

Title: Analysis of convulsant-induced firings in cultured human iPS cell-derived neurons using deep learning

Authors: *N. MATSUDA[1], A. ODAWARA[1,2,3], A. OKAMURA[4], K. KINOSHITA[4], T. SHIRAKAWA[4,5], I. SUZUKI[1,5]
[1]Grad. department of electronics, Tohoku Instititute of Technol., Sendai-Shi, Japan; [2]Aimr, Tohoku Univ., Miyagi, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan; [4]Astellas Pharma Inc., Tokyo, Japan; [5]Consortium for Safety Assessment using Human iPS Cells (CSAHi), Tokyo, Japan

Abstract: Multi-electrode (MEA) assays using human induced pluripotent stem cell (hiPSC)-derived neurons are expected to predict the convulsion, which is one of severe neurotoxicity in drug development. However, an evaluation index of toxicity and differences in responsiveness depending on the convulsant type are not well known. In this study, we aimed to develop an analytical method enabling the evaluation of toxicity and the classification of action mechanism of convulsants using deep learning. hiPSC-derived cerebral cortical neurons were cultured on MEA chips, and the pharmacological responses of 17 drugs in spontaneous firings were obtained by the 24-wells MEA system (Presto). We constructed the raster plots of spontaneous firing and the divided image data. The 4096 feature quantities of the divvied image data in raster plots were extracted by unsupervised learning. Next, feature quantities and drug name were learned by deep learning. Using this learned neuronal network, we have succeeded in separating the responses between non-convulsive drugs and convulsants, the dose-responses, and classifying the action mechanism of convulsive drugs. We also found that there is an effective bin size of image data in raster plots for separating action mechanisms. The artificial intelligence analysis method of

image data in raster plots are useful for an evaluation index of toxicity and classification of action mechanism in MEA data of in vitro cultured hiPSC-derived neuronal networks.

Disclosures: **N. Matsuda:** 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.; Astellas Pharma Inc. **A. Odawara:** 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.; Astellas Pharma Inc. **A. Okamura:** 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.; Astellas Pharma Inc. **K. Kinoshita:** 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.; Astellas Pharma Inc. **T. Shirakawa:** 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.; Astellas Pharma Inc. **I. Suzuki:** 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.; Astellas Pharma Inc..

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.05/LLL8

Topic: I.04. Physiological Methods

Support: AMED Grant 17935517

Title: Drug-induced seizure activities depending on the ratio of excitatory / inhibitory neurons in cultured human iPSC-derived neurons

Authors: ***R. YOKOI**[1], N. MATSUDA[1], Y. ISHIBASHI[1], A. ODAWARA[1,2,3], I. SUZUKI[1,4,5]
[1]Tohoku Inst. of Technol., Sendai-Shi, Japan; [2]Tohoku Univ. ,AIMR, Sendai, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan; [4]iPS-non-Clinical Experiments for Nervous Syst. Project, Tokyo, Japan; [5]Consortium for Safety Assessment using Human iPS Cells, Tokyo, Japan

Abstract: Human induced pluripotent stem cell (iPSC)-derived neurons are promising for evaluating the toxicity of pharmacological agents in nonclinical studies. One of the major

adverse events affecting the central nervous system observed during clinical trials is convulsions. We previously reported the convulsive response using Multi-electrode array (MEA) in cultured hiPC-derived neurons. Although the balance between excitatory and inhibitory inputs is important in convulsive seizure, the optimal proportion of excitatory and inhibitory neurons of human iPS cell-derived neurons in the evaluation assay of drug-induced convulsion toxicity is not known. In this study, we aimed to examine the feature of spontaneous firings and the drug - induced seizure activities depending on the ratio of excitatory/inhibitory neurons in human iPSC-derived neurons. hiPSC-derived cortical neurons, in which the ratio of Glutamatergic and GABAergic neurons are from 8 : 2 to 2 : 8 were cultured on MEA chips, and the spontaneous firings and pharmacological responses of convulsants were obtained by the 24-wells 384 ch MEA system (Presto). The neuronal network with a high percentage of excitatory neurons showed short synchronized burst firings (SBFs) at high frequencies and the firing rate other than SBFs was also high. On the other hand, the network with high inhibitory neurons showed the SBF with long period. In drug-induced seizure activities, there was no remarkable dose responses in high percentage of excitatory neurons, the network with high inhibitory neurons also showed significant activity changes in convulsants other than the inhibitors of GABA receptor. The network with high inhibitory neurons also showed activity change at low concentrations. These results suggest that a higher proportion of GABA neurons is more effective in detecting drug-induced seizure toxicity.

Disclosures: R. Yokoi: None. **N. Matsuda:** None. **Y. IshiBAshi:** None. **A. Odawara:** None. **I. Suzuki:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.06/LLL9

Topic: I.04. Physiological Methods

Title: Real-time measurement of dopamine release in cultured human iPS cell-derived dopaminergic neurons using carbon nanotube MEA system

Authors: *S. NOJI[1], N. MATSUDA[1], A. ODAWARA[1,2,3], I. SUZUKI[1]
[1]Tohoku Inst. of Technol., Sendai-Shi, Japan; [2]Aimr, Tohoku Univ., Sendai-Shi, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan

Abstract: Multi-electrode (MEA) assays using human induced pluripotent stem cell (hiPSC)-derived neurons are expected to predict the toxicity and the pharmacological effects. If we can measure the release of neurotransmitter using this MEA, it is possible to evaluate the drug related to release of neurotransmitters, and it is expected to improve the accuracy of medicinal effects. In this study, we aimed to develop the carbon nanotube (CNT) MEA chip, which enables real-

time measurement of neurotransmitters by electrochemical reaction. The CNT-MEA chip was fabricated by electro-plating method. Detection sensitivity to dopamine (DA) in the fabricated CNT-MEA chip was examined by electrochemical measurement method. The change of DA release to methamphetamine (MTH) were measured using mounted striatal slice of 6 weeks old mice and cultured human iPSC-derived dopamine neurons on CNT-MEA. As a result of the electrochemical measurement, an oxidation peak current was observed at 0.25 V, and the detection limit and linearity of DA was less than 5 nM. We have succeeded in real time detection of DA release using striatal slices and human iPS cell derived DA neurons, and detected the changes in the amount of DA release depending on MTH dose. Furthermore, in the human iPSC-derived DA neuron, a change of spike pattern at MTH administration was detected by conventional filed potential measurement. In summary, we developed a novel CNT-MEA chip having high sensitivity to DA and enabling the detection of DA release from brain slices and cultured hiPSC-derived neuronal networks. We also found that CNT-MEA is possible to both electrochemical measurement of DA release and conventional field potential measurement. CNT-MEA is expected as a new MEA measurement method that improves the accuracy of toxicity prediction and the pharmacological effects.

Disclosures: S. Noji: None. **N. Matsuda:** None. **A. Odawara:** None. **I. Suzuki:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.07/LLL10

Topic: I.04. Physiological Methods

Support: AMED Grant 17bk0104076h0101

Title: Trial for drug-induced seizure liability evaluation using microelectrode array and primary rodent neurons: Multi-site pilot study ofHESI NeuToxMEA subteam

Authors: *N. MIYAMOTO[1], A. OJIMA[2], S. INABA[2], T. YOSHINAGA[1]
[1]EISAI Co., Ltd., TSUKUBA, Japan; [2]Tsukuba branch, Techno Pro R&D company, Techno Pro Inc., Tsuchiura, Japan

Abstract: Drug-induced seizures are a serious cause of drug withdrawal from the market. There is no good non-clinical *in vitro* model to predict seizure liability of drug candidates. Translational Biomarkers of Neurotoxicity (NeuTox) Committee of Health and Environmental Science Institute (HESI) initiated the NeuTox Micro-Electrode Array (MEA) Subteam to investigate use of MEA technology for the prediction of seizure liability of drugs. The team launched a multi-site pilot study and is promoting engagement in scientific discussion utilizing the results of the multi-site pilot study. Because the experimental protocol and significant assay

endpoints have not been standardized yet, each facility is making a presentation in support of the discussion one at a time. Primary cortical neurons were prepared from fetal Wistar rats 18 days post-coitum and seeded on 48-well Classic MEA plates and 24-well MED-Q2430M plates for extracellular recording using Maestro and Maestro Pro or using MED64-Prest respectively. Twelve compounds (pentylenetetrazole; PTZ, picrotoxin; PT, 4-aminopyrdine; 4-AP, linopyridine; LP, amoxapine; AXA, strychnine; SC, pilocarpine; PC, amoxicillin; AXI, chlorpromazine, enoxacin, phenytoin and acetaminophen) were added to the cells (n = 6) at 5 concentrations for each compound to see phenotypic changes on spontaneous electrical activity in neural networks consisting of action potential spikes and organized patterns of synchronized bursts after 19 days of culture. Using data from Maestro and Maestro Pro, we examined 12 metrics: weighted mean firing rate (MFR), number of bursts (NB), burst duration, number of spikes per burst (NS/B), number of network bursts (NNB), network burst duration (NBD), number of spikes per network burst (NS/NB), inter-spike interval coefficient of variation (ISICV), inter-burst interval (IBI), IBI coefficient of variation, network IBI coefficient of variation, etc., to assess the degree of significance for assay endpoints, which are correlated across seizurogenic compounds in the test set. Specific enhancements were observed in MFR, NS/B and NS/NB for $GABA_AR$ inhibitors (PTZ and PT); in MFR, NB and NNB for K^+ channel inhibitors (4-AP and LP); in MFR, NS/B, NS/NB and ISICV for AXA; in NS/B, NS/NB and ISICV for SC; in NBD for PC and in IBI for AXI. In conclusion, there wasn't a common significant endpoint for all seizurogenic compounds, but it seems that there was a specific combination of endpoints for each type of seizurogenic compound. Principal component analysis for several burst parameters, using MED64 Prest data, is underway with the goal of finding useful endpoints for drug-induced epileptogenic phenotype classification.

Disclosures: **A. Ojima:** A. Employment/Salary (full or part-time):; Techno Pro R&D company, Techno Pro Inc. **S. Inaba:** A. Employment/Salary (full or part-time):; Techno Pro R&D company, Techno Pro Inc. **T. Yoshinaga:** A. Employment/Salary (full or part-time):; Eisai Co., Ltd..

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.08/LLL11

Topic: I.04. Physiological Methods

Support: AMED17935517

Title: The evaluation of drug-induced seizure activities using MEA system in cultured human iPSC-derived neurons : Pilot study of HESI NeuTox MEA subteam

Authors: *I. SUZUKI[1], A. ODAWARA[1,2,3], N. MATSUDA[1], Y. ISHIBASHI[1]
[1]Tohoku Inst. of Technol., Sendai, Miyagi, Japan; [2]Tohoku Univ., Sendai Miyagi, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan

Abstract: Human induced pluripotent stem cell-derived neurons are promising for use in toxicity evaluations in nonclinical studies. One of the major adverse events affecting the central nervous system observed during clinical trials is convulsions. Micro-electrode array (MEA) systems have recently attracted attention for use in evaluating the convulsion potential of a drug because they non-invasively measure the electrophysiological activity of neural networks at multiple sites in a high-throughput manner. MEA subteam of Neurotoxicity (NeuTox) Committee in Health and Environmental Science Institute (HESI) initiated the NeuTox Micro-Electrode Array (MEA) Subteam started pilot study using MEA for the prediction of seizure liability of drugs. Human iPSC-derived cortical neurons (Axol) were cultured on 24-wells MEA plate for extracellular recording using Presto. Twelve compounds (pentylenetetrazole, picrotoxin, 4-aminopyrdine, linopyridine, amoxapine, strychnine, pilocarpine, amoxicillin, chlorpromazine, enoxacin, phenytoin and acetaminophen) were tested at 5 concentrations for each compound. Using spontaneous firings data to drug administration, we identified the parameter sets that can separate the responses between convulsive drugs and negative control, and the responses among the several convulsants with different action mechanism using principal component analysis over 10 parameters. We also extracted the 4096 feature quantities from a image data in raster plots by unsupervised learning and constructed the artificial intelligence, in which feature quantities and drug name were learned by deep learning. Using this learned neuronal network, we have succeeded in separating the responses between non-convulsive drugs and convulsants and classifying the action mechanism of convulsive drugs. These our analysis method will be effective for detecting convulsive response and predicting mechanism of action of convulsive drugs.

Disclosures: A. Odawara: None. **N. Matsuda:** None. **Y. Ishibashi:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.09/LLL12

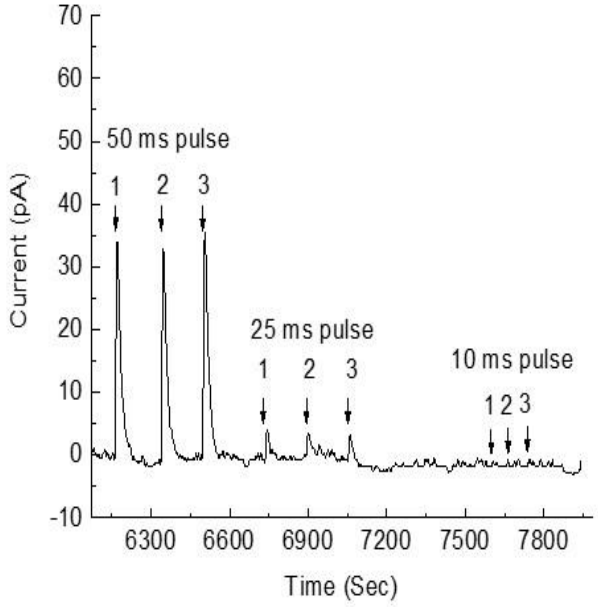
Topic: I.04. Physiological Methods

Support: NSF EPSCoR RII-2 FEC OIA1632891

Title: Glutamate detection in real time with novel microelectrode for *ex vivo* recording

Authors: C. TAN[1], P. T. DOUGHTY[2], N. J. UDSTAD[2], C. D. PERNICI[2], S. SIDDIQUI[1], P. U. ARUMUGAM[1], *T. A. MURRAY[2]
[1]Inst. for Micromanufacturing, [2]Biomed. Engin., Louisiana Tech. Univ., Ruston, LA

Abstract: Few methods are available to quantify local glutamate release dynamics in animal models of disease, especially long term. An enzyme-based platinum microelectrode array (Pt-MEA) built on a ceramic probe has improved spatiotemporal resolution v. single-site probes and microdialysis. We produced Glu microprobes by coating R1 (CenMeT) Pt-MEAs with L-glutamate oxidase (GluOx), bovine serum albumin, and glutaraldehyde and then electrochemically depositing m-phenylenediamine, a size-exclusion polymer for blocking interferents (cycled 20 min, +0.25 V to +0.75 V, 50 mV/s). GluOx produces at the Pt electrode when Glu diffuses out of active synapses; the resulting current from H_2O_2 evolution was plotted in real time. Microprobe performance was tested by electrically stimulating release of Glu from mouse brain slices. Brains were harvested according to an approved IACUC protocol. Single, coronal slices were placed in a brain slice chamber. Microprobes were placed into neocortical locations or CA1 and 100-μA direct current pulses were delivered to tissue within 300 μm of the microprobe. Current returned to baseline between pulses. The peak current for single 1-s pulses was ~70 pA and 100 pA for paired pulses 2 s apart. Current was consistent at each pulse width and scaled with pulse width (Fig 1). This novel Glu microprobe facilitates real time measurements of extracellular Glu level dynamics and will be useful for understanding physiological processes. Next, we will optimize and modify the microprobe for studying glutamate and other neurochemical dynamics *in vivo*.
Funding from NSF EPSCoR RII-2 FEC OIA1632891
Fig 1. Current versus time for 3 stimulations at 3 pulse widths (one channel shown). Peak current scaled with pulse widths from 1 s (not shown) through 25 ms and was consistent at each pulse width. The 10-ms pulses did not elicit measurable glutamate release. The 25-ms pulses resulted in a mean ± SEM peak current of 3.56 ± 0.10 pA. Based on a calibration curve established prior to the measurements, this current corresponds to 468 ± 13 nM glutamate.



Disclosures: C. Tan: None. **P.T. Doughty:** None. **N.J. Udstad:** None. **C.D. Pernici:** None. **S. Siddiqui:** None. **P.U. Arumugam:** None. **T.A. Murray:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.10/LLL13

Topic: I.04. Physiological Methods

Title: A high throughput acute slice micro-electrode array assay for toxicology screening

Authors: *G. CHENG[1], S. NOJI[2], S. YASUOKA[3], R. ARANT[4], M. TRUJILLO[5], I. SUZUKI[2]
[1]Alpha Med. Scientific Inc./ Automate Scientific Inc, Berkeley, CA; [2]Tohoku Inst. of Technol., Miyagi, Japan; [3]Alpha Med. Scientific Inc., Osaka, Japan; [4]Alpha MED Scientific, Inc., Osaka, Japan; [5]Alpha MED Scientific Inc., Osaka, Japan

Abstract: Micro-electrode arrays (MEAs) are an established instrument for measuring neuronal and cardiac electrophysiological activity in vitro. The power of MEAs lend themselves to applications that can be applied to drug discovery, safety pharmacology, and toxicology screening. The present study demonstrates the power of a high-sensitivity MEA engineered for acute brain slices in improving the efficacy and accuracy of neurotoxicity screening in acute hippocampal slice preparations from mice. We demonstrate the capabilities of the highly

sensitive MED64-Quad system, a novel medium-throughput MEA engineered for acute or cultured slice applications in assessing neurotoxicology risk from acute mouse brain slices. Acute hippocampal slices from 6-8 week old mice were assessed for seizurogenic -like activity in response to compounds that are likely to elicit synchronized network activity typical of seizure-like activity (convulsants). We measured network burst activity and decomposed frequency analysis of field potential oscillations (analogous to EEG) in response to compounds known to elicit seizure-like activity. Spontaneous firing rate, synchronized network bursts, and the decomposed frequency component of the local field potential were measured in response to 4-Aminopiridine, Pentylenetetrazole, Picrotoxin, Pilocaprine and Strychnine. We demonstrate the power of the MED64-Quad system in detecting several measures of synchronized burst activity including the duration of synchronized bursts, total spikes within a burst, inter-burst interval, co-efficient of variation for the inter-peak interval of bursts, and the co-efficient of variation for the speak spikes of synchronized bursts. The results of this study indicated that the MED64-Quad system increases throughput while maintaining high enough sensitivity to detect spontaneous spiking, synchronized network bursts, and epileptiform activity in response to convulsants. The MED64-Quad MEA is a useful tool for improving the accuracy, efficacy, and throughput of drug discovery, target validation, safety pharmacology, and toxicology screening.

Disclosures: G. Cheng: None. **S. Noji:** None. **S. Yasuoka:** None. **R. Arant:** None. **M. Trujillo:** None. **I. Suzuki:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.11/LLL14

Topic: I.04. Physiological Methods

Support: German Research Foundation (DFG): SFB 1233, Robust Vision: Inference Principles and Neural Mechanisms, TP 14

Title: Artificial stimulation at user-defined cell positions following electrical imaging using CMOS-based high-density microelectrode arrays

Authors: *A. CORNA[1], M. REH[2], D. HOFFMANN[2], F. JETTER[2], M. KRIEBEL[2], G. ZECK[2]
[1]Univ. of Tübingen, Ctr. for Ophthalmology, Tuebingen, Germany; [2]Neurophysics, Natural and Med. Sci. Inst. (NMI) at the Univ. of Tübingen, Reutlingen, Germany

Abstract: When recording or modulating activity in neural networks it is of great advantage to obtain precise information about soma location, about subcellular compartments and about putative synaptically connected cells.
Here we present an algorithm for automated identification of cell locations in ex vivo retinal

networks and in dissociated neuronal cultures. The two neural systems were interfaced to high-density CMOS-based MEAs. The algorithm computes the spike triggered average (STAs) electrical image and performs a classification of the electrical images during the experiment. This enabled us to selectively stimulate cells at user-specified locations.
Two types of artificial stimulation will be presented. First, electrical stimulation was performed using a subset of 1024 available stimulation sites of the CMOS MEA. Stimulation waveforms could be selected to either activate axons or to avoid this activation. Secondly, optogenetic stimulation of channelrhodopsin-transduced cells revealed precise spiking. Precise adjustment of the stimulation intensity could be used to selectively stimulate cell subpopulations. The presented experiments demonstrate the power of electrical imaging using high-density microelectrode arrays prior to artificial stimulation.

Disclosures: A. Corna: None. **M. Reh:** None. **D. Hoffmann:** None. **F. Jetter:** None. **M. Kriebel:** None. **G. Zeck:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.12/LLL15

Topic: I.04. Physiological Methods

Support: Federal Ministry of Education and 285 Research (BMBF funding number 13GW0033B)
Federal Ministry for Economic Affairs 286 and Energy (BMWi) and the European Social Fund (ESF) (funding number 03EFJBE108 287 EXIST)

Title: PEDOT polymer electrodes for non-invasive 8 channel full band DC EEG recordings from freely moving piglets and sports horses

Authors: *N. V. DE CAMP[1,2], J. BERGELER[3]
[1]Vet. Medicine,Physiology, Free Univ. Berlin, Humboldt Univ. Berlin, Berlin, Germany; [2]Physiol., Med. Ctr. of the Johannes Gutenberg Univ. Mainz, Mainz, Germany; [3]Vet. Medicine, Physiol., Free Univ. Berlin, Med. Ctr. of the JGU Mainz, Berlin, Mainz, Germany

Abstract: We invented the first non-metallic, self-adhesive and dry biosignalling electrode. The Poly(3,4-ethylenedioxythiophene) (PEDOT) polymer electrode changes its aggregate state and conductivity by light curing. The electrode can be applied underneath hair without shaving. With the aid of blue light, the electrode can be hardened within a few seconds at the desired location. The cured polymer electrode is highly conductive and can be applied on a very small location. Unlike other EEG electrodes, our electrode does not lose conductivity upon drying. The electrode strongly bonds to skin and does not require any additional adhesive. Short circuits due

to an outflow of gel are prevented with this technique. Therefore, the PEDOT polymer electrode is extremely well suited for applications that, up to now, have been challenging, such as non-invasive EEG recordings from awake and freely moving animals, EEG recordings from preterm babies in the neonatal intensive care unit or long-term recordings in the case of sleep monitoring or epilepsy diagnostics. We tested the PEDOT Polymer electrode with sleep recordings from piglets and sports horses. Typical patterns like spindle bursts and K-Komplexes can be identified with the new technique.

Disclosures: N.V. De Camp: None. **J. Bergeler:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.13/LLL16

Topic: I.04. Physiological Methods

Support: Swedish Scientific Research Council Grant 2014-2048
Göran Gustafsson Memorial Foundation
Swedish Scientific Research Council Grant 2016-02184

Title: Long-term high-density extracellular recordings enable studies of muscle cell physiology and pathology

Authors: M. LEWANDOWSKA[1], E. BOGATIKOV[1], A. HIERLEMANN[2], *A. R. PUNGA[1]
[1]Neurosci., Uppsala Univ., Uppsala, Sweden; [2]Dept. of Biosystems Sci. and Engin., ETH Zürich, Basel, Switzerland

Abstract: Skeletal (voluntary) muscle is the most abundant tissue in the body, thus making it an important biomedical research subject. Studies of neuromuscular transmission, including disorders of defective ion channels or receptors in autoimmune or genetic neuromuscular disorders, require high spatial resolution and an ability to acquire repeated recordings over time in order to track pharmacological interventions. Preclinical techniques for studying diseases of neuromuscular transmission can be enhanced by physiologic *ex vivo* models of tissue-tissue and cell-cell interactions. We present a method, which we used to follow the development of primary skeletal muscle cells from myoblasts into mature contracting myofibers over more than two months. In contrast to most previous studies, the muscles do not detach from the surface but instead form functional networks between the myofibers, whose electrical signals we observed over the entire culturing period. Primary cultures of mouse myoblasts differentiated into contracting myofibers on a chip that contains an array of 26,400 platinum electrodes at a density of 3,265 electrodes per mm^2. Our ability to track extracellular action potentials at subcellular resolution enables discovery of the origin of possible failure mechanisms in muscle diseases.

This system in turn enables creation of a novel electrophysiological platform for establishing *ex vivo* disease models.

Disclosures: M. Lewandowska: None. **E. Bogatikov:** None. **A. Hierlemann:** None. **A.R. Punga:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.14/LLL17

Topic: I.04. Physiological Methods

Support: Pilot Project Award from the Hope Center for Neurological Disorders at Washington University

Title: Sensory percepts elicited by macrosieve stimulation of peripheral nerve: A rat behavioral model

Authors: N. S. CHANDRA[1], W. M. MCCARRON[3], H. BURTON[4], *D. W. MORAN[1], L. S. GREEN[2], W. Z. RAY[5], M. R. MACEWAN[5]
[1]Dept. of Biomed. Engin., [2]Dept. of Psychological and Brain Sci., Washington Univ., Saint Louis, MO; [4]Neurosci., [5]Dept. of Neurosurg., [3]Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: The macrosieve electrode (MSE) is a highly stable implant that interfaces with peripheral nerve and uses advanced current steering to selectively recruit subfascicular axon clusters with wide nerve coverage. The MSE might be an optimal platform for introducing sensory feedback (via interfaced peripheral nerve) that originates in embedded sensors in a prosthetic limb. To investigate this possibility, we developed a rat behavioral model to evaluate the MSE's ability to elicit sensory percepts at low current amplitudes without damaging nerve tissue over multiple activation cycles. Six adult, male Lewis rats learned a go/no-go auditory detection task. Training occurred in a sound- and light-attenuating Skinner box equipped with a house light, tone generator (2,900 Hz), snout detector and food-dispenser. Each rat learned to initiate trials by inserting its snout into the detector. The rat had to maintain snout insertion for a randomized interval (4 ± 2 s) to receive an auditory stimulus. Next, the snout had to be withdrawn from the detector within 500 ms of stimulus onset to receive reinforcement. Premature withdrawal (prior to stimulus onset) extinguished the house light for a 10 s time out as punishment. Late withdrawal (> 500 ms after stimulus onset) resulted in a 5-s inter-trial interval. After successfully learning to detect the auditory stimulus, five of the rats underwent a sterile surgery for implantation of an MSE. After induction of anesthesia, we exposed the right sciatic nerve, transected it, and sutured the proximal and distal stumps into a pair of silicone guidance conduits affixed to a prepared MSE/Omnetics assembly. The Omnetics connector, with trailing

microwires, was routed subcutaneously to the skull, passed through a scalp incision, and embedded in an acrylic head-cap. The connector provides an external interface to the MSE during behavioral experiments. Rats with implanted MSEs remained stable for 4-12 months following surgery; this interval is sufficient for relearning a go/no-go analog of the auditory detection task by attending stimulation of the sciatic nerve now activated through the implanted MSE. Current success with an implanted MSE in several rats will advance the development of sensory feedback originating from embedded sensors in prosthetic limbs and represent the potential of a clinically viable sensory interface.

Disclosures: N.S. Chandra: None. **W.M. McCarron:** None. **H. Burton:** None. **D.W. Moran:** None. **L.S. Green:** None. **W.Z. Ray:** None. **M.R. MacEwan:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.15/LLL18

Topic: I.04. Physiological Methods

Support: DARPA Grant HR0011-15-2-0006

Title: Reliability and acute *in vivo* testing of the lyse-and-attract cuff electrode

Authors: *C. LARSON, S. ELYAHOODAYAN, A. COBO, K. SCHOLTEN, D. SONG, E. MENG
Biomed. Engin., USC, Los Angeles, CA

Abstract: A major obstacle barring clinical implementation of peripheral nerve (PN) interfaces is the dual requirement to maintain long-term health of the nerve while still targeting specific nerve fibers. Our minimally invasive approach integrates microfluidic channels into an extraneural PN cuff for targeted delivery of a lyse-and-attract drug regimen to intact nerve. Collagenase delivery lyses connective tissue layers then neurotrophic growth factor induces sprouting of nerve fibers. The anticipated result is proximity of the nerve fibers to the electrodes for increased selectivity and signal fidelity without invading the PN bundle.
The lyse-and-attract cuff electrode (LACE) is microfabricated as a compliant sheet of Parylene C polymer with embedded platinum electrodes. Integrated design features include microfluidic channels with embedded electrodes and a ratchet-type locking mechanism to secure the cuff around the nerve. We evaluate reliability of the LACE under simulated *in vivo* conditions and report preliminary results from acute *in vivo* animal studies, including the first report of localized lysing of epineurium on live nerve through an extraneural cuff.
LACE were soaked in phosphate-buffered saline at 37 °C (one month) to simulate *in vivo* conditions. Periodic electrochemical impedance spectroscopy and interelectrode crosstalk testing

was performed. After two weeks, electrode impedance at 1 kHz decreased from 2.5 to 2.1 kΩ, while average signal leakage between electrodes remained below 10%. After one month, impedance decreased to 1.0 kΩ and signal leakage ranged from 10 to 63%, suggesting some delamination of the insulation. This suggests suitability of the current design for in vivo studies up to two weeks and that additional improvement to the fabrication process is required to achieve chronic reliability attained in neural interfaces of similar construction.
LACE were applied *in vivo* to rat sciatic nerve. Compound action potentials (CAP) were recorded by LACE arising from monophasic bipolar stimulation (200 μs, 5–150 μA) applied using implanted needle electrodes. Stimulation was repeated following application of lidocaine. Recordings prior to lidocaine captured CAP, but after lidocaine captured only the stimulus artifact. For lysing, 1 μL of collagenase was delivered through the LACE at 100 μL/min. Each nerve was then explanted, sectioned, and imaged. Histology sections near the microchannel outlets revealed lysed regions of the epineurium while sections away from the outlets showed no evidence of lysing. These results successfully demonstrate the functionality of the LACE device and potential of the LACE drug delivery approach.

Disclosures: C. Larson: None. **S. Elyahoodayan:** None. **A. Cobo:** None. **K. Scholten:** None. **D. Song:** None. **E. Meng:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.16/LLL19

Topic: I.04. Physiological Methods

Support: DGIST R&D Program of the Ministry of Science, ICT and Future Planning (17-BD-0401)

Title: Functional electrical stimulation of ischemic stroke rat

Authors: *C. SONG, C. YEO
DGIST, Daegu, Korea, Republic of

Abstract: Rehabilitation effects of functional electrical stimulation have been studied in animal model and human, for treating various diseases such as spinal cord injury (SCI) and stroke disease. Percutaneous and implant FES configuration capable of activating deep muscles and placing electrodes in same position repeatedly and appropriately, has been spotlighted to improve the effectiveness of FES. However, the validation from animal experiment is essential because these invasive approaches are hard to apply human directly. Although rodent model has been used with low cost and easy to access, most of the studies focused on SCI rodent model. The studies for stroke rodent model are relatively less. Most FES studies with rodent model

showed therapeutic effectiveness of electrical stimulation rather than function stimulation to assist their voluntary mobility. The goal of this study is to develop FES pattern capable of inducing gait motion in ischemic stroke rat model, with percutaneous FES configuration. The Animal Experiment Ethics Committee of Daegu Gyeongbuk Institute of Science and Technology approved the experimental protocol (approval no. DGIST-IACUC-17102520-00). All ischemic stroke rats were induced by the surgery of middle cerebral artery occlusion. In hind-limb stimulation, the electrodes were inserted into quadriceps and hamstring muscles on left and right legs to induce walking motion. In upper-limb stimulation, the electrodes were placed only on left side induced ischemic stroke. For shoulder movement, unilateral spinodeltoideus and supraspinatus were stimulated. To induce elbow and digit movement, the electrodes were inserted in triceps/biceps and extensor digitorum communis/flexor digitorum profundus muscles. Electrical parameters were set to biphasic asymmetric wave, frequency of 75 Hz, pulse widths of 200 usec/phase, and pulse with of 0.25 ~ 1 mA. When the movement induced by FES are compared between before and after stroke, stiff movement after stroke was shown because of hemiplegia. It requires accurate parameter tuning for assisting more natural movement in step with rat's intention. We try to find optimal stimulation parameters and conditions for inducing natural movement. These works may contribute to the studies of implant FES system and neuronal stimulation for stroke rehabilitation of human.

Disclosures: C. Song: None. **C. Yeo:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.17/LLL20

Topic: I.04. Physiological Methods

Support: DARPA contract N66001-17-C-4013

Title: A transdural very-near field wireless power and data link for implantable neural interfaces

Authors: *M. P. POWELL[1], D. A. BORTON[1,2,3]
[1]Sch. of Engin., [2]Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [3]Ctr. for Neurorestoration and Neurotechnology, Dept. of Veterans Affairs, Providence Med. Ctr., Providence, RI

Abstract: Traditional microelectrode arrays (MEAs) capable of electrical access to the brain with single cell resolution must communicate with external electronics via a wire tether through the dura matter. This physical connection is non-trivial to implant, results in chronic perforation of the dura, and may affect the stability of neural recordings as the tether mechanically perturbs the MEA. Completely untethered, "floating", neural interfaces have been developed but are often

limited in their ability to transfer sufficient power to the implant while maintaining high data rates for transmitting neural data. Improving the performance of the wireless link will enable higher channel counts and the ability to include more advanced electronic payloads allowing for new experimental paradigms. To address these challenges, a very-near field transdural wireless link is proposed for communicating power and data to an untethered floating neural implant. Inductive coupling is commonly used to power biomedical implants, but link design often focuses on optimizing power transfer over long distances and in weakly coupled systems. By reducing the wireless transmission distance, link performance and efficiency can be improved over such designs. We present a system capable of delivering 15 mW of power to a centimeter scale device with 57% efficiency. Additionally, the link is robust to coil misalignments of up to 3 mm. Power management circuitry provides a constant DC voltage supply for on-board components. To stream full broadband neural data from the implant, a previously designed RF application specific integrated circuit (ASIC) was used in conjunction with a field programmable gate array (FPGA) and a software defined radio (SDR) based receiver. Data rates of approximately 4.3 Mbps were achieved. Improvements on the data transmission circuitry are proposed with a target data rate of &gt10 Mbps. In addition, a circuit design is presented that can extract a clock from the power signal, preventing the need for on-implant clock synthesis. An optimized power amplifier will improve overall system efficiency for wireless power delivery and amplitude modulation can be used at the transmitter to deliver forward data to the implant. By implementing a very-near field wireless link, many of the traditional design limitations for a floating implant are lifted enabling, for example, on-implant recording, stimulation, and signal processing capabilities for low latency closed loop experiments. Other system architects could leverage the designs presented here to develop low power, untethered neural technologies without sacrificing advanced features.

Disclosures: M.P. Powell: None. **D.A. Borton:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.18/LLL21

Topic: I.04. Physiological Methods

Support: NSF GRFP Grant DGE 1321851
Citizens United for Research in Epilepsy Taking Flight Award
Neil and Barbara Smit Fund

Title: Transparent graphene electrodes for high resolution *in vivo* optical and electrophysiological mapping of epileptic networks

Authors: *N. DRISCOLL[1], H. TAKANO[3], B. MURPHY[4], R. VISHNUBHOTLA[5], D. A. COULTER[3], A. JOHNSON[5], B. LITT[4], F. VITALE[2]
[1]Bioengineering, Univ. of Pennsylvania, Ambler, PA; [2]Ctr. for Neuroengineering and Therapeut., Univ. of Pennsylvania, Philadelphia, PA; [3]Pediatrics Div. of Neurol., Children's Hosp. of Philadelphia, Philadelphia, PA; [4]Bioengineering, Univ. of Pennsylvania, Philadelphia, PA; [5]Physics, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Of the estimated 50 million people worldwide currently living with epilepsy, approximately one-third do not achieve seizure freedom from antiepileptic drugs. For these patients, the only hope is highly targeted clinical intervention either with resective surgery or neuromodulation therapy. Yet, there are not currently robust methods for mapping epileptic circuits *in vivo* at high resolution and correctly identifying the areas to resect or stimulate. Events such as spikes and high frequency oscillations (HFOs) inform clinical decision making in identifying epileptic networks and seizure onset regions, but their actual size and dynamics are not well understood, particularly down at the cellular level. Experiments with high resolution electrophysiology and optical imaging in animal models have begun to shed light on these network dynamics, but they are limited: optical methods, like calcium imaging, can identify activity at the cellular level, but their temporal resolution is not sufficient to record epileptic biomarkers, such as HFOs. Electrophysiology has superior temporal resolution, but tissue sampling is limited to the regions around individual electrodes.
In this work, we present a platform for simultaneous *in vivo* optical and electrical recording based on transparent, flexible graphene electrode arrays and apply our technology to map epileptic networks, HFOs and seizure spread in an acute murine model of epilepsy induced by application of 4-aminopyridine (4-AP). The micro-electrode arrays demonstrated here consist of a 3x3 grid of 50x50 μm^2 graphene contacts embedded in a parylene-C substrate. The devices are >90% optically transparent across the visible and NIR spectrum, and chemically doped to achieve 1 kHz impedance of 1.34 ± 0.22 MΩ. We recorded 4-AP-induced seizure activity simultaneously on the graphene electrodes and through calcium epifluorescence imaging in anesthetized GCaMP6-exresssing mice (Jax #025776, Jackson Laboratory). We observed localized foci generating interictal HFOs and analyzed their spatio-temporal relationship to seizure onset and spread *in vivo*. We also detected on the electrodes spatial patterns of seizure onset and propagation corresponding to patterns of activity emerging in calcium imaging, and distinct electrographic patterns corresponding to different spatial patterns of seizure propagation, including planar and spiral waves. We plan to expand on this work by performing cellular-resolution imaging using two-photon imaging to elucidate the dynamics of seizure dynamics at the cellular level.

Disclosures: N. Driscoll: None. **H. Takano:** None. **B. Murphy:** None. **R. Vishnubhotla:** None. **D.A. Coulter:** None. **A. Johnson:** None. **B. Litt:** None. **F. Vitale:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.19/LLL22

Topic: I.04. Physiological Methods

Title: Epidermal electrotherapy for epilepsy

Authors: *S.-W. PARK[1,2], J. KIM[1], M. KANG[1], W. LEE[1], B. PARK[2], H. KIM[2], S.-Y. CHOI[3], S. YANG[4], J.-H. AHN[1], S. YANG[2]
[1]Yonsei Univ., Seoul, Korea, Republic of; [2]Incheon Natl. Univ., Incheon, Korea, Republic of; [3]Seoul Natl. Univ. Sch. of Dent., Seoul, Korea, Republic of; [4]City Univ. of Hong Kong, Kowlong, Hong Kong

Abstract: Penetrating electronics have been used for treating epilepsy, yet their therapeutic effects are debated largely due to the lack of a large scale, real-time, safe recording/stimulation. Here, our proposed technology integrates ultrathin and flexible epidermal electronics into an electrocorticography (ECoG) array, therein simultaneously sampling brain signals in a large area for diagnostic purposes and delivering electrical pulses for treatment. The system was empirically tested to record the ictal-like activities of the thalamocortical network in vitro and in vivo using our epidermal electronics. Furthermore, the electronics selectively diminished epileptiform activities but not normal signal transduction. We propose that this technology heralds a new generation of diagnostic and therapeutic brain-machine interfaces. Such an electronic system can be applicable for several brain diseases such as tinnitus, Parkinson's disease, Huntington's disease, depression, and schizophrenia

Disclosures: S. Park: None. **J. Kim:** None. **M. Kang:** None. **W. Lee:** None. **B. Park:** None. **H. Kim:** None. **S. Choi:** None. **S. Yang:** None. **J. Ahn:** None. **S. Yang:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.20/LLL23

Topic: I.04. Physiological Methods

Support: Wellcome Trust

Title: Paired recordings using high-density CMOS probes and patch-clamp: A ground-truth dataset and an experiment in collaboration

Authors: *A. MARQUES SMITH[1], J. NETO[1], J. NOGUEIRA[1], L. CALCATERRA[1], D. KIM[1], G. DIMITRIADIS[1], A. R. KAMPFF[1], G. LOPES[2], J. FRAZAO[3]
[1]Sainsbury Wellcome Ctr., [2]Univ. Col. London, London, United Kingdom; [3]2Champalimaud Neurosci. Programme, Champalimaud Ctr. for the Unknown, Lisbon, Portugal

Abstract: We built a rig to perform paired patch-clamp and extracellular recordings from the same neuron *in vivo.* In this setup, the axes of two micromanipulators are precisely aligned and their relative position is tracked in real-time by Bonsai software, allowing us to accurately target patch-clamp recordings to neurons near the extracellular probe. We used this approach to generate a publicly-available dataset where a cortical neuron's spiking activity is recorded on a dense CMOS probe and compared to its counterpart acquired through a patch-clamp electrode. "Ground-truth" datasets of this kind are rare but valuable to the neuroscience community, as they power the development and improvement of spike-sorting and analysis algorithms, tethering them to empirical observations. First, we describe our approach and report exploratory and descriptive analysis on this dataset. We study the detectability of patch-clamp spikes on the extracellular probe, manual clustering of paired spikes based on ground-truth features, within-unit reliability of spike features and spatiotemporal dynamics of the action potential waveform. Second, we propose a GitHub-based platform to host, accelerate and improve further work undertaken by others and ourselves on this dataset, including but not restricted to spike-sorting algorithm benchmarking. We suggest guidelines and best-practise workflows in a guise to stimulate transparency, replicability, real-time peer-review and accurate credit assignment.

Disclosures: A. Marques Smith: None. **J. Neto:** None. **J. Nogueira:** None. **L. Calcaterra:** None. **D. Kim:** None. **G. Dimitriadis:** None. **A.R. Kampff:** None. **G. Lopes:** None. **J. Frazao:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.21/LLL24

Topic: I.04. Physiological Methods

Support: NIH Grant R01DC014044 (MH)
NIH Grant R24NS086603 (MH)
NIH Grant R01DC13412 (DM)

Title: Fabrication, testing, and refinement of a silicon-based cochlear nucleus array

Authors: *N. NOLTA[1], P. GHELICH[1], M. JACOBS[1], D. B. MCCREERY[2], M. HAN[1]
[1]Biomed. Engin. Dept., Univ. of Connecticut, Storrs, CT; [2]Neural Engin. Program, Huntington Med. Res. Inst., Pasadena, CA

Abstract: In this poster we describe the fabrication, *in vivo* testing, and ongoing refinements of a silicon-based neural recording and stimulation electrode array. The array has iridium electrode sites, metal interconnects, and silicon oxide/silicon nitride passivation layers. Deep reactive ion etching is used to define electrode shanks. Backside thinning by reactive ion etching allows the probes to be released from the silicon-on-insulator wafer. Mechanical grinding of the probe tips results in a sharp, pointed tip, rather than a vertical wedge. Finally, cleaning, packaging, and sterilization complete the device. *In vivo* testing efforts have focused on using this array as part of an auditory brainstem implant in cats. The sharp tips and sturdy shanks facilitated successful implantation into the cochlear nucleus and inferior colliculus with an inserter tool. The 3D multi-shank layout of the electrode sites allowed for tonotopic stimulation at different locations in the cochlear nucleus. The arrays have performed successfully *in vivo* for over one year. These studies suggest the arrays could be used in a hearing prosthesis for people with deafness who cannot benefit from a cochlear implant due to ossified cochlea or damaged auditory nerves. Other applications could include closed-loop deep brain stimulation, spinal cord stimulation, and other difficult-to-reach anatomical targets where 3D multi-shank layout, mechanical robustness, and stable long-term performance are desired. Finally, we present preliminary work on novel refinements in the fabrication process such as recessed metal interconnects.

Disclosures: N. Nolta: None. **P. Ghelich:** None. **M. Jacobs:** None. **D.B. McCreery:** None. **M. Han:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.22/LLL25

Topic: I.04. Physiological Methods

Support: DARPA TNT N66001-17-2-4010

Title: Examination of the neurobiological mechanisms underlying Vagus Nerve stimulation in a non-human primate

Authors: A. J. SUMINSKI[1], A. Z. RAJALA[2], J. P. NESS[3], C. FILLA[3], D. GWOZDZ[3], E. MUELLER[3], J. R. NOVELLO[4], S. HURLEY[3], W. ZENG[3], W. LAKE[3], *L. C. POPULIN[5]
[1]Dept. of Neurolog. Surgery, Univ. of Wisconsin-Madison, Madison, WI; [2]Univ. of Wisconsin, Madison, Madison, WI; [3]Univ. of Wisconsin, Madison, WI; [4]Univ. of Wisconsin, madison, WI; [5]Dept of Neurosci., Univ. Wisconsin, Madison, WI

Abstract: Electrical stimulation of peripheral nerves is an effective method to influence, modulate, or change the function of the nervous system in a controlled and timely manner. The technique holds great potential to treat various conditions, and to change/improve normal cognitive functions such as learning, memory and decision-making. Vagus nerve stimulation (VNS) is perhaps the most widely used, but the underlying mechanisms of action are not well understood. Here, we present the first steps toward the development of a comprehensive approach to study the neurobiological mechanisms underlying VNS in a non-human primate preparation. One Rhesus monkey (Macaca mulatta, 6.5 yrs old) weighing 11.8 kg was induced with ketamine (10 mg/kg), intubated and anesthetized with 1.5% isoflurane for the duration of the experiment. The local IACUC approved all procedures. Buprenorphine (0.01 mg/kg) was given prior to surgery for analgesia. Heart rate, respiratory rate, blood pressure, oxygen saturation and temperature were monitored throughout the procedure. Under sterile surgical conditions, the cervical vagus nerve was exposed using blunt dissection and separate stimulating (2mm ID, 7mm inter-electrode spacing, LivaNova Inc) and recording (2mm ID, 2mm inter-electrode spacing) bipolar, cuff electrodes were implanted (1.5cm separation). A pair of needle electrodes implanted in the sternocleidomastoid (SCM) monitored electromyographic (EMG) activity evoked by stimulation. Following surgery, the subject was placed prone to facilitate measurement of pupil fluctuations resulting from VNS using an Eyelink 1000Plus (SR Research). Electrical stimulation of the vagus was performed using trains of 16 biphasic (cathode leading) pulses (0.8mA, 100us per phase) at five frequencies ranging from 7Hz to 110Hz. We observed a reliable, stimulation locked decrease in respiration rate and modulation in SCM EMG in response to VNS verifying engagement between the stimulating electrode and nerve. Importantly, these responses were eliminated by transecting the nerve proximally and distally to the cuff electrodes. Future work will examine the effects of VNS on compound nerve action potentials and pupil diameter fluctuations in awake, behaving subjects.

Disclosures: A.J. Suminski: None. **A.Z. Rajala:** None. **J.P. Ness:** None. **C. Filla:** None. **D. Gwozdz:** None. **E. Mueller:** None. **J.R. Novello:** None. **S. Hurley:** None. **W. Zeng:** None. **W. Lake:** None. **L.C. Populin:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.23/LLL26

Topic: I.04. Physiological Methods

Support: DARPA TNT N66001-17-2-4010

Title: Evaluation of neural interfaces for electrical stimulation of the rat trigeminal nerve

Authors: *A. J. SUMINSKI[1], J. P. NESS[2], W. ZENG[3], J. NOVELLO[2], S. K. BRODNICK[2], J. PISANIELLO[2], A. M. DINGLE[3], S. O. POORE[3], W. B. LAKE[1], J. C. WILLIAMS[2]
[1]Dept. of Neurolog. Surgery, [2]Dept. of Biomed. Engin., [3]Surgery, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Over the past decade, electrical stimulation of various cranial nerves has been shown to be an effective adjunctive therapy for many diseases including epilepsy and depression. Furthermore, these techniques hold great promise to treat other conditions and modulate cognitive functions such as learning, memory and decision-making. While the vagus nerve has traditionally been the target of these therapies, recent preclinical data suggests that the trigeminal nerve may present an alternative option due to is superficial course and integration with the sympathetic and parasympathetic nervous systems. However, the mechanism of action trigeminal nerve stimulation (TNS) remains in question. In this work, we describe the development and evaluation of a neural interface targeting the rat trigeminal nerve with the goal of enabling future mechanistic research on TNS. Fifteen (n=15) Lewis rats we used in experiments designed to: 1) identify the best stimulation target(s) for TNS in the rat and 2) evaluate the ability of a cuff electrode to stimulate the nerves. Using fresh cadavers (n=5), we investigated the course and measured the size of each branch of the trigeminal nerve, and found that both the V1 (supraorbital) and V2 (infraorbital) branches were best candidates for a neural interface to their accessibility and size (0.57 +/- 0.14 mm and 2.83 +/- 0.22 mm diameter, respectively). To evaluate the methodology to engage the branches of the trigeminal nerve, Lewis rats were anesthetized with isoflurane (1-2.5%) and implanted with a custom bipolar cuff electrode on the infraorbital nerve distal to the infraorbital foramen (1.5mm ID, 0.05mm wire diameter; n=5) or supraorbital nerve (0.75mm ID, 0.05mm wire diameter; n=5). Electrical stimulation was performed using single, monophasic or biphasic (cathode leading) pulses (50-800uA, 100-300us per phase) initiated at pseudorandom intervals (varying between 3-4 seconds). We measured changes in cortical activity in the barrel cortex elicited by infraorbital stimulation using a custom 16 channel uECoG array (200um site diameter, 500um inter-electrode spacing). Similarly, we measured changes in the orbicularis oculi electroromyogram elicited by infraorbital stimulation to verify engagement of the supraorbital nerve. In both cases stimulation evoked activity increased monotonically until saturation with increases in stimulation current and activation thresholds decreased with increases in phase duration. These preliminary results suggest that supraorbital and infraorbital nerve interfaces are suitable candidates for examining the neural mechanisms of TNS in the rat.

Disclosures: A.J. Suminski: None. **J.P. Ness:** None. **W. Zeng:** None. **J. Novello:** None. **S.K. Brodnick:** None. **J. Pisaniello:** None. **A.M. Dingle:** None. **S.O. Poore:** None. **W.B. Lake:** None. **J.C. Williams:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.24/LLL27

Topic: I.04. Physiological Methods

Support: NSF Grant 1345215

Title: Development of nanoelectrodes array using iridium oxide/gold nanowires for fast imaging of neural network

Authors: *H. YOON, M. H. KIM, A. SHIMKEVITCH, S. HAN, M. FREEMAN
Norfolk State Univ., Norfolk, VA

Abstract: It is critically important to develop highly and reliably performing electrodes for fast imaging of neural activity using electrical impedance tomography in chronic experiments. For fast electrical impedance tomography (fEIT) imaging of neural network, electrochemical properties of electrodes including impedance spectrum determines spatial and temporal resolution of imaging. In this research, vertically aligned iridium oxide/gold nanowire (IrOx/AuNW) electrodes with low impedance values were developed with the diameters of 280 μm for temporal resolution of 30 msec and 200 μm resolution imaging in the brain. For testing of long term stability of electrodes, electrochemical impedances were measured under 1 million cycles of current injection with 1725 Hz frequency and their variation of electrochemical properties was analyzed to determine effect of current injection on developed electrodes. The results show the stability of electrodes up to the level of 1 mA current injection, which is a sufficient level of electrode performance for fEIT. In addition, electrode potential drift effects were also measured and analyzed with various current injection conditions. This research demonstrated that novel IrOx/AuNW electrodes array can highly perform fEIT imaging for neural network in the brain for long term.

Disclosures: H. Yoon: None. **M.H. Kim:** None. **A. Shimkevitch:** None. **S. Han:** None. **M. Freeman:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.25/LLL28

Topic: I.04. Physiological Methods

Support: NIH Grant R21EY028397A
DARPA Young Investigator Award
Welch Foundation
Dan Duncan Postdoctoral Fellowship

Title: Microfluidic implantation of multi-channel flexible electrodes for neural recording

Authors: *A. V. RODRIGUEZ[1], B. FAN[2], D. G. VERCOSA[3], C. KEMERE[4], J. T. ROBINSON[1]
[1]Electrical and Computer Engin., [2]Dept. of Electrical and Computer Engin., [3]Dept. of Applied Physics, [4]Rice Univ., Houston, TX

Abstract: Ultra-small, flexible neural electrodes with diameters the size of individual cells significantly increase the quality and longevity of neural recordings by reducing neural injury during chronic implantation. However, these flexible electrodes are traditionally difficult to implant and position without causing acute damage. Researchers typically apply stiffening agents that temporarily increase the overall size and rigidity of the electrode in order to overcome the buckling force upon implantation, but these methods increase the electrode footprint and cause increased acute damage and potentially chronic damage. Previously, we have demonstrated a novel, minimally invasive method of implanting flexible electrodes through the use of a fluidic microdrive designed to prevent buckling and drive electrodes into the brain without the need for stiffening agents. Using specially designed vent channels and viscous drive fluid, we are able to minimize the amount of fluid directed towards the brain, preventing additional trauma during implantation. Here, we show improvements upon the original design of the microdrive which allow for preconnected multi-channel flexible electrodes to be implanted into the rat brain without the need for stiffening agents or rigid shuttles. Current work focuses on comparing long term immune response and unit stability of flexible electrodes implanted with the fluidic microdrive versus more traditional methods.

Disclosures: A.V. Rodriguez: None. **B. Fan:** None. **D.G. Vercosa:** None. **C. Kemere:** None. **J.T. Robinson:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.26/LLL29

Topic: I.04. Physiological Methods

Support: This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) Biological Technologies Office (BTO) ElectRX program under the auspices of Dr. Eric Van Gieson through DARPA Contracts Management Office Contract No. HR0011-16-C-0094

Title: Neural implant insertion system using ultrasonic micro-vibration to improve penetrating microelectrode array insertion mechanics: *In vitro* and *in vivo* evaluations

Authors: *R. S. CLEMENT, N. N. TIRKO, J. K. GREASER, C. A. SCRUGGS, T. J. HIGGINS, R. B. BAGWELL
Res. and Develop., Actuated Med. Inc., Bellefonte, PA

Abstract: Penetrating electrode arrays provide localized access to neural stimulation and recording sources, and are a valuable neuroscience research tool. Neuroscientists and researchers developing future clinical applications continually seek to increase information transfer potential by implanting electrode arrays with higher numbers of shanks at greater density. Successful insertion of penetrating electrode arrays into brain tissue remains a significant challenge, and outcomes are often heavily reliant on surgical skill and technique. During insertion, electrode arrays apply forces to the neural tissue resulting in significant compression (dimpling) at the implant site and strain on local tissues. Shallow insertions (< 1 mm) targeting the upper cortical layers are especially difficult. The electrode array may need to be over-inserted past the target depth to ensure puncture of meningeal membranes, or be fired in at very high velocity, limiting implantation accuracy and possibly increasing implantation trauma. To combat these challenges, we have developed a penetrating electrode array inserter that utilizes ultrasonic micro-vibration to improve insertion mechanics. The inserter system incorporates a piezoelectric transducer, operated in an axial resonant mode, which transmits high-frequency micro-vibrations to an attached electrode array via a reversible coupler mechanism. Previously we have demonstrated the system could insert custom-built 2x4 fixed microwire (dia: 50 µm) arrays with lower peak forces (~78% difference) in agar brain model and *ex vivo* rodent brain, and with lower dimpling (~80% difference) of brain surface *in vivo*, as compared to non-vibrated insertion (speed= 50 µm/s). The ultrasonic micro-vibration does not appear to be harmful to neurons, as neural activity can be recorded immediately post-insertion and for weeks following implant. More recently we have evaluated the system for insertion of 2x8 microwire (dia: 65 µm) arrays obtained from a commercial provider (Tucker-Davis Technologies). Ultrasonic micro-vibration enables the reliable insertion of the arrays even through the dura, significantly simplifying surgical procedures. High quality neural recordings are observed immediately and for weeks following implant surgery. Ongoing studies are evaluating the performance of arrays implanted with ultrasonic micro-vibration for up to 4-6 weeks, followed by an assessment of post-implant histology. Reducing array implantation trauma and improving the electrode placement process is critical to maximize chronic neural interface performance, and future clinical translation of neural implant systems.

Disclosures: **N.N. Tirko:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **J.K. Greaser:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **C.A. Scruggs:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc. **T.J. Higgins:** A.

Employment/Salary (full or part-time):; Actuated Medical, Inc. **R.B. Bagwell:** A. Employment/Salary (full or part-time):; Actuated Medical, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actuated Medical, Inc..

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.27/LLL30

Topic: I.04. Physiological Methods

Support: Starkey Hearing Technologies Research Grant

Title: Effects of cerumen and electrodermal response on in-ear electroencephalography

Authors: *A. PAUL[1], S. R. DEISS[2], D. TOURTELOTTE[3], G. CAUWENBERGHS[4]
[1]Univ. of California San Diego, La Jolla, CA; [2]Inst. for Neural Computation, UC San Diego, La Jolla, CA; [3]Starkey Hearing Technologies, Eden Prairie, MN; [4]Dept. of Bioengineering, UCSD, La Jolla, CA

Abstract: Conventional electroencephalography (EEG) requires placement of several electrode sensors on the scalp and, accompanied by lead wires and bulky instrumentation, makes for an uncomfortable experience. Recent efforts in miniaturization and system integration have enabled smaller systems, such as wearable, in-ear EEG devices that are gaining popularity for their unobtrusive form factor. Although in-ear EEG has been demonstrated in recent works, dynamics of the ear and ear canal that directly effect electrophysiological measurements have been largely ignored. Here, we present a quantitative analysis of electrode-skin impedance for in-ear EEG that accounts for cerumen (earwax) and electrodermal response. Custom fitted earmolds with 16 embedded electrodes were developed to map the skin conductance in the ear canal of 3 subjects. In the presence of cerumen, the calculated average conductivity of the ear canal was 73% less than canals removed of cerumen. Electrodermal activity was also found to play a role in electrode-skin impedance, increasing SC by up to 300% in response to certain stimuli. The better understanding of the dynamics of in-ear conditions may improve consistency and accuracy of in-ear electrophysiology.

Disclosures: **A. Paul:** 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.; Starkey Hearing Technologies Grant. **S.R. Deiss:** None. **D. Tourtelotte:** A. Employment/Salary (full or part-time):; Starkey Employee. **G. Cauwenberghs:** None.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.28/LLL31

Topic: I.04. Physiological Methods

Support: NSF 1450467

Title: Low-cost, mobile, and wearable eeg

Authors: *N. BELKAYA, A. RAMAKRISHNAN, M. L. PLATT
Univ. of Pennsylvania, Philadelphia, PA

Abstract: There is a growing interest in the mobile, wearable, and low-cost electro-encephalogram (EEG) devices that can provide research grade signals regarding the brain states of individuals. While scalp EEG has long been the default approach to non-invasively diagnose epilepsy and traumatic brain injury, there is no viable way to continuously tract patients' EEG activity - other than long hospital stays in the wired EEG long-term monitoring unit (LTM), which is expensive and impractical. Aside from diagnosis, mobile EEG devices can lead to the development of continuous healthcare monitoring applications, personalized treatment protocols in medicine and optimal training programs in sports to name a few. With that purpose in mind, we have assembled a new EEG device with novel, flexible, dry electrodes -- that are capable of maintaining electrical contact with the subject's skin in the absence of electrolytic gel. The novel electrodes exhibited minimal signal loss at EEG-level voltage and frequencies. Signals obtained from our dry electrodes were matched in quality with those obtained from the current "gold standard" Ag/AgCl wet electrode. In the long run, as the gel dried up, while the wet electrode signal quality deteriorated, signals from the new electrodes were unaffected. Furthermore, the flexible nature of the electrode helped the sensor adhere to the skin preventing relative electrode-skin movements, which greatly reduced motion artifacts. These features have opened up the avenue to monitor brain states during highly mobile, naturalistic interactions, which are being tested currently. Based on these observations, we believe that the novel technology would be useful to several clinical applications, consumer research, and could open up new markets hitherto unexplored.

Disclosures: **N. Belkaya:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); receipt of intellectual property rights/patent holder. **A. Ramakrishnan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); receipt of intellectual property rights/patent holder. **M.L. Platt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); receipt of intellectual property rights/patent holder.

Poster

700. Physiological Methods: Electrophysiology: Electrode Arrays II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 700.29/LLL32

Topic: I.04. Physiological Methods

Support: NINDS Intramural

Title: Multi-day 24-hour recording from single units in human cortex

Authors: *C. ZAWORA[1], J. H. WITTIG, JR[2], K. A. ZAGHLOUL[3]
[1]Surgical Neurol. Br., NINDS, NIH, Silver Spring, MD; [2]NINDS, Bethesda, MD; [3]Surgical Neurol. Br., Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD

Abstract: Recent advances in human micro-electrode array technology and fully-automated spike sorting methods have opened the door to new analyses of how human neurons respond during cognitive tasks. Despite these breakthroughs, a basic understanding of how soon after implant one should expect to see single units and how the quality and yield of isolated units changes over the course of a typical hospital stay is lacking. Here we recorded spiking neuron activity from microelectrode Utah arrays (Cereplex I; Blackrock Microsystems Inc.) implanted in the surface of the human temporal lobe in 10 epilepsy patients undergoing intracranial monitoring for up to 3 weeks. We first confirmed that a widely-used automated spike-sorting algorithm (Mountainsort, Chung et al. 2017) applied to this unique dataset successfully mimicked manual sorts made on a subset of the data. Next, we used a high-performance computing cluster to sort all recorded channels (either 96 or 192 electrodes), collected 24-hours a day, and applied machine learning algorithms to track whether identified units were dropped or new units were found during the course of the recording (Frasier and Schwartz 2012). Here we present the evolution of single-unit isolation quality and quantity for the first 3 weeks following implantation in a human participant. We evaluate whether population spike rate changes systematically over the days following implantation, and lastly, whether isolation quality, quantity, and spike-rate vary with each participant's circadian rhythm.

Disclosures: C. Zawora: None. **J.H. Wittig:** None. **K.A. Zaghloul:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.01/LLL33

Topic: I.05. Biomarker and Drug Discovery

Support: JSPS KAKENHI grant numbers 23791333 and 26461718
the Research Group for Schizophrenia

Title: The cell cycle-related genes as biomarkers for schizophrenia

Authors: *S. OKAZAKI, S. BOKU, I. OTSUKA, N. EGUCHI, I. SORA, A. HISHIMOTO
Dept. of Psychiatry, Kobe Univ. Grad. Sch. of Med., Kobe, Japan

Abstract: Background: Recent studies suggest that genomic abnormalities such as single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) may elevate the risk of schizophrenia. Such genomic abnormalities often occur during chromosomal DNA replication in the S phase of cell cycle. In addition, several studies showed that abnormal expressions of several cell cycle-related genes are associated with schizophrenia. Therefore, here we compared mRNA expression levels of cell cycle-related genes in peripheral blood cells between patients with schizophrenia and healthy controls.
Methods: mRNA expression levels of cell cycle-related genes in peripheral blood cells from patients with schizophrenia and healthy controls were measured with quantitative reverse transcription polymerase chain reaction (Q-RT-PCR). The discovery, replication and intervention studies with Q-RT-PCR were performed as follows: discovery (40 cases and 20 controls), replication (82 cases and 74 controls) and intervention (22 cases and 18 controls).
Results: Nine genes were identified in the discovery and replication stages as schizophrenia-associated genes. Moreover, the combination of mRNA expression levels of *CDK4*, *MCM7*, and *POLD4* was identified as a potential biomarker for schizophrenia with multivariate logistic regression analysis. The intervention stage revealed thatthe mRNA expression levels of these three genes were significantly decreased in the acute state of schizophrenia, and *CDK4* was significantly recovered in the remission state of schizophrenia.
Conclusions: The combination of mRNA expression levels of three cell cycle-related genes such as *CDK4*, *MCM7*, and *POLD4* is expected to be a candidate for useful biomarkers for schizophrenia. Especially, the mRNA expression changes of *CDK4* may be potential as both trait and state markers for schizophrenia.

Disclosures: S. Okazaki: None. **S. Boku:** None. **I. Otsuka:** None. **N. Eguchi:** None. **I. Sora:** None. **A. Hishimoto:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.02/LLL34

Topic: I.05. Biomarker and Drug Discovery

Support: KAKENHI 16K19189

Title: Plasma brain-type fatty acid-binding protein is a potential candidate biomarker for psychiatric disorders

Authors: *M. KOGA[1,2], S. NAKAGAWA[3,2], A. SATO[2], Y. WAKATSUKI[2], K. KITAGAWA[2], R. KAMEYAMA[2], N. UDO[2], S. ASAKURA[2], Y. FUJII[2], Y. KAKO[2], K. ITO[2], N. MITSUI[2], H. NARITA[2], K. TOYOSHIMA[2], A. KATO[2], I. KUSUMI[2]
[1]Dept. of Psychiatry, Natl. Def. Med. Col., Tokorozawa, Japan; [2]Dept. of Psychiatry, Hokkaido Univ. Grad. Sch. of Med., Sapporo, Japan; [3]Div. of Neuropsychiatry, Dept. of Neurosci., Yamaguchi Univ. Grad. Sch. of Med., Ube, Japan

Abstract: There is urgent need to understand the pathophysiology of psychiatric disorders. To support this, biomarkers correlated with those disorders and symptoms must be identified. Since the organs primarily involved in psychiatric disorders are the brain, a tissue biopsy is generally impossible. Identifying molecules which are released from the abnormal organ and detectable in peripheral tissue such as blood, urine, etc. is a useful approach. However, such kinds of molecules have been poorly identified in psychiatric disorders. Previous studies have reported that elevated serum levels of brain-type fatty acid-binding protein (B-FABP) were observed in patients with dementia and ischemic stroke, thus suggested that B-FABP may be a useful biomarker for neurological disorders and cerebrovascular disorders. Relations between serum or plasma B-FABP levels and psychiatric disorders have not been reported. Although not as obvious levels as in neurodegenerative diseases, an involvement of nerve cell loss and cell death in the pathophysiology of mental disorders have also been reported. We hypothesized that B-FABP would also be a biomarker for psychiatric disorders. Patients with schizophrenia (n=30), bipolar disorder (n=29), depression (n=35), and subjects without a history of a mental disorder (n=40) were recruited. Patients with schizophrenia were evaluated through the Positive And Negative Syndrome Scale (PANSS), and patients with bipolar disorder and depression were evaluated with the Hamilton Depression Rating Scale (HAM-D) and the Young Mania Rating Scale (YMRS). Significantly elevated plasma B-FABP levels were observed in the schizophrenia group (4.87 ± 0.25 pg/mL*), the bipolar group (5.63 ± 0.26 pg/mL*) and the depression group (5.87 ± 0.24 pg/mL*) compared to the control group (2.74 ± 0.22 pg/mL). (*$p<0.0001$ by Tukey-Kramer test). PANSS score was correlated with the plasma B-FABP concentration in the schizophrenia group ($r^2=0.33$, $p=0.0008$). However, HAM-D and YMARS scores in the bipolar

disorders and depression showed no correlation with plasma B-FABP levels. Although the present study suggested that B-FABP may be a useful biomarker for psychiatric disorders, plasma B-FABP concentrations were higher in the all disease groups studied in this study than in the control group, suggesting that it reflects the pathophysiology common to these diseases. Further study would be to clarify the symptoms of psychiatric disorders correlated with plasma B-FABP concentration. This study was approved by the Ethics Committee of Hokkaido University Hospital.

Disclosures: M. Koga: None. **S. Nakagawa:** None. **A. Sato:** None. **Y. Wakatsuki:** None. **K. Kitagawa:** None. **R. Kameyama:** None. **N. Udo:** None. **S. Asakura:** None. **Y. Fujii:** None. **Y. Kako:** None. **K. Ito:** None. **N. Mitsui:** None. **H. Narita:** None. **K. Toyoshima:** None. **A. Kato:** None. **I. Kusumi:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.03/LLL35

Topic: I.05. Biomarker and Drug Discovery

Support: AMED Brain/MINDS

Title: New measurement system for prepulse inhibition of acoustic startle response in common marmosets

Authors: *K. HAZEHARA, K. NAKAMURA
Primate Res. Institute, Kyoto Univ., Inuyama/Aichi, Japan

Abstract: Prepulse inhibition (PPI) is a neurophysiological phenomenon in which a weaker stimulus (prepulse) reduces the startle reflex to a subsequent intense stimulus (pulse). PPI usually occurs when the prepulse precedes the pulse by 30 - 500ms and 60 - 120ms intervals is reported to produce maximal inhibition in rodents and humans. Since PPI deficits in schizophrenia patients was reported in 1978, PPI is used as a biomarker for abnormalities of sensory-motor gating that underlies sensory flooding and cognitive fragmentation in schizophrenia. Common marmosets are suitable as nonhuman primate models concerning human neurologic diseases and psychiatric disorders. Hence objective behavioral indices are necessary to quantitatively assess the severity of symptoms in such models. However, so far, there are no methods to measure acoustic startle response and PPI in marmosets. The appropriate method varies among animal species (e.g., electromyography for orbicularis oculi muscle in humans, accelerometer for whole-body movement on all fours in rodents, and accelerometer in a sitting position in other nonhuman primates). Therefore, we had to choose an appropriate methodology for common marmosets. At first, we chose the method used in nonhuman primate research for marmosets to

quantify acoustic startle response and PPI. However, we failed to measure their startle response. Then, we applied whole-body protocol used in rodent research for marmosets. Our new apparatus consisted of 2 components: a startle response measuring device with a pressure transducer and a cage attached to the device. The device was filled with water. When a marmoset moved in the cage, their startle response was transmitted via water to the pressure transducer. First, we examined whether common marmosets show acoustic startle responses with a sound of 120dB. Of 5 marmosets tested, 4 marmosets but one showed startle responses. We regarded the one marmoset that did not show a startle response as a non-responder. Then, we tested whether the marmosets showed PPI. The 4 marmosets were presented in 4 kinds of trials (pulse-alone, prepulse-alone, PPI at 60ms intervals, PPI at 120ms intervals). 2 marmosets showed significant decreased startle responses in the PPI trials. These results suggest that PPI probably occurred at least in these 2 marmosets. The remaining 2 marmosets may also have shown PPI if we used an appropriate interval in PPI trials or paradigm. Further experimentation is needed to investigate appropriate inter-stimulus intervals for PPI in marmosets. We conclude that we have developed a new measuring system for PPI in common marmosets.

Disclosures: K. Hazehara: None. **K. Nakamura:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.04/LLL36

Topic: I.05. Biomarker and Drug Discovery

Support: JSPS KAKENHI Grant 18H02756
JSPS KAKENHI Grant 18K15534
JSPS KAKENHI Grant 18K07620
Intramural Research Grant (24-11,27-1) for Neurological and Psychiatric Disorders of NCNP
JSPS KAKENHI Grant 25253075
Health and Labour Sciences Research Grants for Comprehensive Research on Persons with Disabilities from Japan Agency for Medical Research and Development, AMED(15dk0310061h0001, 16dk0307062h0001)

Title: Altered cerebrospinal fluid levels of matrix metalloproteinases in mood disorders and schizophrenia

Authors: W. OMORI[1], K. HATTORI[2], M. OKADA-TSUCHIOKA[1], K. ITAGAKI[1], N. KAJITANI[1], H. ABE[1], H. KUNUGI[2], *M. TAKEBAYASHI[1,3]
[1]Natl. Hosp Org Kure Med. Centr, Kure, Hiroshima, Japan; [2]Natl. Ctr. of Neurol. and Psychiatry

Hosp., Tokyo, Japan; [3]Dept. of Neuropsychiatry Fac. of Life Science, Kumamoto Univ., Kumamoto, Japan

Abstract: [Background] Matrix metalloproteinases (MMPs) are extracellular proteases involved in neuron / glia plasticity and inflammatory processes. We found a significant alteration of serum levels of MMP-2 in a state-dependent manner among patients with major depressive disorder (MDD) (Shibasaki et al., 2016). However, whether blood concentrations of MMP reflect the function in the brain is unclear. Therefore, MMPs in mood disorders and schizophrenia were examined using cerebrospinal fluid (CSF) in the current study. [Method] CSF was obtained from Japanese patients with MDD, bipolar disorder, and schizophrenia (SCZ) and from age- and gender-matched healthy controls (HC). First, MMP-1, 2, 3, 7, 8, 9, 10, 12, 13 were measured using Bio-Plex Pro Human MMP Assays (9-Plex) in small samples. Since MMP-3, 9, 12, 13 levels were almost equal to zero, CSF levels of the remaining MMPs, MMP-1, 2, 7, 8, 10, were measured in patients with MDD (n = 90), bipolar disorder (n=59), SCZ (n = 86), and HC (n = 106) using Bio-Plex Pro Human MMP Assays (5-Plex). Depressive symptoms were evaluated using the Hamilton Depression Rating Scale score. Psychotic symptoms were evaluated using Positive and Negative Syndrome Scale. The ethics committee of the national center of neurology and psychiatry (NCNP) and national hospital organization (NHO) Kure medical center approved the protocol of this study. All participants provided written consent. [Results] CSF level of MMP-2 was detectable in all samples, but MMP-1 level was almost equal to zero while the MMP-7, 8, 10 levels were much lower (average 14.5pg/ml, 19.4pg/ml, 28.9pg/ml, respectively) compared to MMP-2 level (average 5.96ng/ml). Therefore, we focused on MMP-2 level. In all samples, the correlation between MMP-2 level and age ($p<0.001$) was positive, and the difference between men and women ($p<0.001$) was significant. Thus, we compared the MMP-2 level while adjusting for age and gender between groups. As a result, a significant increase was found in patients with MDD (average 6.20ng/ml, $p=0.023$) and with SCZ (average 6.15ng/ml, $p=0.030$) compared to HC (average 5.57ng/ml). Additionally, a significant positive correlation emerged between MMP-2 level and depressive symptoms in MDD ($p=0.045$) while MMP-2 levels and psychotic symptoms in SCZ did not correlate ($p=0.174$). Finally, correlation between MMP-2 levels and imipramine equivalent doses of antidepressants in patients with MDD was non-significant ($p=0.691$). [Conclusion] We found a significant increase of CSF levels of MMP-2 in a state-dependent manner among patients with MDD, suggesting that MMP-2 may be related to the pathophysiology of MDD.

Disclosures: W. Omori: None. **K. Hattori:** None. **M. Okada-Tsuchioka:** None. **K. Itagaki:** None. **N. Kajitani:** None. **H. Abe:** None. **H. Kunugi:** None. **M. Takebayashi:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.05/LLL37

Topic: I.05. Biomarker and Drug Discovery

Support: JSPS KAKENHI
CREST-JST toS.U.
Grant for The industrial Strategic Research and Development from Yamaguchi Prefecture to H.Y.
Academic research support of MSD

Title: The potential usefulness of long noncoding RNAs as biomarkers of major depressive disorder

Authors: *T. SEKI, H. YAMAGATA, S. UCHIDA, C. CHEN, K. HARADA, K. MATSUO, Y. WATANABE, S. NAKAGAWA
Yamaguchi Univ. Sch. of Med., Ube Yamaguchi, Japan

Abstract: There is growing evidence suggesting that aberrant transcription regulation plays a critical role in the pathophysiology of major depressive disorder (MDD). Although long noncoding RNAs (lncRNAs) have important functions in the chromatin structure, gene expression, and subsequent manifestation of various biological processes in the central nervous system, it is still unclear whether the aberrant expression of lncRNAs is involved in MDD. We therefore investigated the usefulness of lncRNAs as biomarkers of MDD. In Experiment 1, using gene expression microarray analysis, we comprehensively searched gene expressions that are changing in a stress-dependent manner in the hippocampus, the prefrontal cortex and the blood of chronically stress-loaded BALB / c mice. In Experiment 2, we compared the expression of lncRNAs in the blood of 29 currently depressed human patients suffering from MDD with 29 health controls, who were matched for age and sex. This study was approved by the Institutional Review Board of Yamaguchi University Hospital and written informed consent was obtained from all participants after providing them with a complete description of the study. We measured the expression levels of 84 lncRNAs in the blood leukocytes of depressed patients and healthy controls using a quantitative real-time PCR analysis. The results of the two experiments indicated several differentially expressed lncRNAs in stressed mice and depressed patients as compared to control mice and human subjects. Thus our data support the usefulness of blood lncRNAs as potential biomarkers for MDD.

Disclosures: T. Seki: None. **H. Yamagata:** None. **S. Uchida:** None. **C. Chen:** None. **K. Harada:** None. **K. Matsuo:** None. **Y. Watanabe:** None. **S. Nakagawa:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.06/LLL38

Topic: I.05. Biomarker and Drug Discovery

Support: NIH Grant T32 MH016259
Veterans Affairs 1IK2BX002823
Veterans Affairs CDA BX002130

Title: Serine racemase knockout mice demonstrate schizophrenia-like EEG biomarker deficits

Authors: *D. D. AGUILAR, M. R. ZIELINSKI, J. M. MCNALLY
Psychiatry, VABHS, Harvard Med. Sch., West Roxbury, MA

Abstract: Many noninvasive techniques are being explored as potential biomarkers for developing psychosis. Abnormalities in spontaneous and task-evoked gamma oscillations, sensory gating, processing of a deviant stimuli [(mismatch negativity (MMN)] and/or entrainment to a 40Hz auditory stimulus [auditory steady state response (ASSR)] have been observed in schizophrenia (Sz) patients and in others with clinical high risk to transition to psychosis. Further, a number of these biomarkers are associated with cognitive processes impaired in this disorder. Converging evidence suggests NMDA receptor hypofunction is central to the pathophysiology of Sz and other severe psychiatric disorders, and likely contributes to impairments in these translationally relevant biomarkers. NMDA receptor function has been indirectly linked to abnormalities in MMN, ASSR, and spontaneous gamma power, but their underlying mechanisms are not completely understood.

Here we have examined this relationship utilizing the serine racemase knockout (SR KO) mouse model, which has been shown to demonstrate Sz-like NMDA receptor hypofunction, and a variety of cognitive impairments. Adult male SR KO mice (n=4) and WT controls (n=3) were used for *in vivo* EEG/EMG recordings to test the translationally-relevant biomarkers listed above. EEG electrodes were stereotaxically implanted above the frontal and parietal cortices. In brief: 40 Hz ASSR was evoked using 1 second 90 dB click trains (100 repetitions), sensory gating used paired 4 kHz tones (50ms each, 500ms apart, 100 repetitions), and MMN used a 1Hz train of 9 identical tones (2 kHz pitch) followed by a deviant tone (4 kHz, 100 reps).

In the ASSR, a 40Hz auditory stimulus evoked an increase in 40Hz cortical power for WT but not SR KO mice. In sensory gating, the second tone had a reduced attenuation in gamma power in KO animals (32% attenuation of 1st tone) compared to WT (57%). In the MMN, the deviant tone evoked a large evoked response potential around 150ms in WT but not SR KO mice. We observed no changes in spontaneous gamma oscillation power.

In conclusion, SR KO mice demonstrated a variety of Sz-like deficits in EEG biomarkers, creating a logical association between these biomarkers and impaired NMDA receptor function. Interestingly, certain phenotypes like increased spontaneous gamma band connectivity are observed in first episode stages of psychosis but may be less common with disease progression (*Di Lorenzo et al 2015 Front Hum Neurosci*). These mice could be useful for exploring the underlying mechanisms behind these biomarkers and testing potential therapies for the cognitive and auditory deficits associated with these abnormal biomarkers.

Disclosures: D.D. Aguilar: None. **M.R. Zielinski:** None. **J.M. McNally:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.07/LLL39

Topic: I.05. Biomarker and Drug Discovery

Support: Burroughs Wellcome Fund Career Award at the Scientific Interface
NSF CBET1605679
NSF EF1724026
NSF IGERT Competitive Innovation Fund

Title: An *in vivo* automated functional screening method identifies modulators of neural activity for accelerated drug discovery

Authors: *R. LAGOY, D. ALBRECHT
Biomed. Engin., Worcester Polytechnic Inst., Worcester, MA

Abstract: Mental health disorders affect one in six adults in the U.S. and altered neural activity is believed to be an underlying symptom, sometimes with known genetic causes. Most prescribed therapeutics that aim to treat these disorders are not effective and have severe side effects, likely due to indirect and off-target compound interactions. Therefore, the identification of therapeutics that act with high specificity to restore function *in vivo* should yield improved treatments for neural activity-dependent diseases. Automated functional screening technologies are particularly useful for identifying compounds that modulate neural activity. However, these methods are currently limited to *in vitro* assays which do not consider multicellular interactions, and therefore lead to treatments that have substantial systemic effects *in vivo*.
To identify more effective therapeutics, we developed an automated high-content functional screening technology to assess long-term compound effects *in vivo* using the model organism *C. elegans*. The nematode *C. elegans* is transparent, small, and genetically tractable, allowing for both stimulation and recording of neural activity in large isogenic populations. Our method enables fast, simple, and cost-effective immobilization of >15,000 animals distributed evenly across 384-well plates, in which ~40 animals per well are exposed to a particular compound condition for over 18 to 24 hours. We screened 640 FDA-approved drugs for changes to stimulated neural responses in >33,000 living animals across two fully-automated experiments in less than one week. Of the several primary hits, we found that felodipine, a voltage-gated calcium channel (VGCC) blocker, suppresses neural activity in *C. elegans* over 6-18 hours of exposure. Interestingly, this compound does not cause severe developmental effects in the worm, unlike other VGCC antagonists, suggesting that it may have greater specificity for the nervous system. Using this method, we also systematically characterized the time course and bioavailability of various compounds in *C. elegans*, such as All-*Trans* Retinal that is required for

optogenetic experiments in nematodes.
Taken together, we expect that our method will accelerate the identification of more effective therapeutics for activity-dependent disorders by directly identifying compounds that modulate cellular activity *in vivo*. In the future, we also plan to screen for modulators of intercellular communication in *C. elegans* and further characterize our primary hits for use in secondary screens and translational studies involving mammalian systems and disease models.

Disclosures: R. Lagoy: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property rights/patent holder. **D. Albrecht:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property rights/patent holder.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.08/LLL40

Topic: I.05. Biomarker and Drug Discovery

Title: Auditory steady state responses (ASSRs) in awake-behaving primates: A translatable biomarker for drug-discovery in schizophrenia

Authors: *B. J. HANSEN[1], S. J. TYE[1], A. MANOHAR[2], M. J. MARINO[2], J. M. USLANER[2], D. A. HENZE[1]
[1]In Vivo Pharmacol., [2]Neurosci., Merck Res. Labs., West Point, PA

Abstract: A robust pathophysiological finding related to schizophrenia is dysfunction of parvalbumin positive (PV+) interneurons. Numerous post mortem studies have identified a loss of GABAergic markers related to a decrease in PV+ cell function. PV+ cells also referred to as "Fast-spiking interneurons" are characterized by sustained high-frequency spiking activity in response to strong inputs and their ability to respond to such input with minimal delay. It is this unique combination of biophysical properties that suggests PV+ cells underlie gamma band oscillations (GBOs), which have been reported to be deficient in schizophrenic patients. GBOs are hypothesized to play a critical role in cognitive processing, which is supported by studies where disruption in PV+ cell activity decreases GBOs and impairs cognition. Clinically, one of the most consistent biomarkers used in the assessment of schizophrenia is Auditory Steady State Responses (ASSRs). During this procedure amplitude-modulated tones are presented at a rhythm in the gamma range (e.g. 40Hz) while cortical electroencephalograms (EEGs) are measured to analyze gamma power and phase synchronization. It is has recently been suggested that the stimulus-driven changes in GBOs during ASSRs are the result of an increase in PV+ cell activity. Surprisingly, there has been little if any preclinical work exploring ASSRs and GBOs in

awake-behaving primates, which are an ideal animal model that can provide objective and quantifiable results while taking advantage of more complex behavioral testing. We have developed a novel and highly translatable paradigm to record quantitative electroencephalography (qEEG) activity in primates during periodic auditory stimulation. Briefly, 10 male rhesus macaques (Macaca mulatta) were trained to sit quietly in a study chair in a custom sound-attenuated chamber and exposed to a series of 500ms white-noise tones presented at 30 or 40Hz. We assessed spectral power using the continuous wavelet transform and phase synchronization using inter-trial coherence (ITC) analyzed 200ms after stimulus onset to 500ms and ± 5 Hz around the tone frequency. All data were pre-processed and analyzed using custom software coded and complied in Matlab. Gamma power and inter-trial phase coherence of ASSRs were altered following treatments with the NMDA antagonist ketamine at ~10% of the anaesthetic dose. This allows us to explore the mechanisms underlying schizophrenia-like symptoms and assess the role of novel compounds and their influence on cognitive processing in a large animal species in a preclinical setting.

Disclosures: B.J. Hansen: A. Employment/Salary (full or part-time):; Merck & Co., Inc. **S.J. Tye:** A. Employment/Salary (full or part-time):; Merck & Co., Inc. **A. Manohar:** A. Employment/Salary (full or part-time):; Merck & Co., Inc. **M.J. Marino:** A. Employment/Salary (full or part-time):; Merck & Co., Inc. **J.M. Uslaner:** A. Employment/Salary (full or part-time):; Merck & Co., Inc. **D.A. Henze:** A. Employment/Salary (full or part-time):; Merck & Co., Inc..

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.09/LLL41

Topic: I.05. Biomarker and Drug Discovery

Support: NIH Grant R21MH095644
Stanley Medical Research Institute Grant 03-484
Stanley Medical Research Institute Grant 06T-797
Psychoactive Drug Screening Program, PDSP. NIH Contract HHSN-271-2013-00017-C

Title: Mitochondrial Translocator Protein (TSPO) binding: A common occurrence in CNS-active plant species used in Peruvian traditional medicine

Authors: *C. GALLO[1], G. POLETTI[2], R. ROJAS[2], A. VAISBERG[2]
[2]Laboratorios de Investigación y Desarrollo, [1]Univ. Peruana Cayetano Heredia, Lima, Peru

Abstract: The mitochondrial translocator protein (TSPO) also known as peripheral-type benzodiazepine receptor is a yet poorly understood protein, which seems to be involved in a

range of functions that span from acting as a housekeeping gene to its participation in the adaptations to stress and the modulation of mood and cognition. At molecular level TSPO promotes the transport of cholesterol across mitochondrial membranes and may play a role in lipid metabolism, although it is apparently not required for steroid hormone biosynthesis. In the CNS, TSPO is expressed both in neurons and in glial cells.
Ethanol extracts (n=477) from plant collections corresponding to 265 species from 87 different plant families were tested for TSPO binding, using [3H]PK11195 as ligand, in the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill (UNC). This repository of ethanol extracts was generated through the collection of information on the traditional use of plants for the treatment of brain disorders in several Peruvian localities and geographical regions.
A total of 176 of the assayed extracts (37%) showed 50% or higher inhibition of [3H]PK11195 binding. Further studies will let us determine the nature of this binding, regarding to an agonist or antagonist action on TSPO function.
The main traditional uses reported for these 176 extracts are: for nerves/madness/schizophrenia (84 mentions), for depression/sadness/ tiredness/cheering up/getting vigorous (50 mentions), for insomnia/ tranquilizer/sedative/anxiety/stress (31 mentions).
Noteworthy, recent studies show that TSPO levels are lower across several brain regions in patients with first-episode psychosis and schizophrenia compared with healthy controls. Also, TSPO ligands have shown to reduce depression and anxiety in rodents.
Our plant extracts are a unique source of novel molecules with TSPO ligand properties which merit additional studies.

Disclosures: C. Gallo: None. **G. Poletti:** None. **R. Rojas:** None. **A. Vaisberg:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.10/LLL42

Topic: I.05. Biomarker and Drug Discovery

Support: Sardinia Region Grant F72F16002850002
Fondazione di Sardegna Grant F71I17000200002

Title: The neurosteroid allopregnanolone mediates sensorimotor gating deficits induced by D1 receptor activation

Authors: *F. TRACCIS[1], L. J. MOSHER[2], S. FANNI[1], P. SABA[1], G. GIUA[1], P. DEVOTO[1], M. BORTOLATO[2], R. FRAU[1,3,4,5]
[1]Dep. Biomed. Sciences, Div. Neurosci. and Clin. Pharmacol., Univ. of Cagliari, Cagliari, Italy;

[2]Pharmacol. and Toxicology, Univ. of Utah, Salt Lake City, UT; [3]Tourette Syndrome Ctr., Cagliari, Italy; [4]Sleep Med. Ctr., Cagliari, Italy; [5]Natl. Inst. of Neurosci. (INN), Cagliari, Italy

Abstract: Sensorimotor gating, the information-processing function aimed at filtering out irrelevant or superfluous information, is differentially modulated by dopamine. Accordingly, the best-validated operational index of sensorimotor gating, the prepulse inhibition (PPI) of the acoustic startle, is impaired by D_1 receptor agonists in C57BL/6 mice, but not in Sprague-Dawley rats. We previously showed that the dopaminergic regulation of PPI is moderated by 5α-reductase, the enzyme catalyzing the rate-limiting step of neurosteroid synthesis. Here we show that C57BL/6 mice with a nonsense mutation of the enzyme 5α-reductase 1 (5αR1) are insensitive to the PPI-disrupting effects of the selective D_1 receptor agonist SKF82958 (0.3 mg/kg, IP). The sensitivity of 5αR1 KO mice to the PPI-disruptive effects of D_1 receptor activation was reinstated by administration of the neurosteroid allopregnanolone (AP; 3 mg/kg, IP). Conversely, Sprague-Dawley rats were rendered sensitive to the PPI-disrupting effects of SKF82958 (0.05 mg/kg, IP) by administration of AP in the prefrontal cortex (PFC) or sleep deprivation, a manipulation that increases AP levels in the PFC. Taken together, these results show that AP is necessary and sufficient to enable the sensitivity of D_1 dopamine receptor activation with respect to PPI, and may help explain how stress may modulate dopaminergic sensitivity in sensorimotor gating. Future studies will be needed to study whether differences in AP levels in the brain may be responsible for the different sensitivity of PPI to the effects of D_1 receptor agonists.

Disclosures: F. Traccis: None. **L.J. Mosher:** None. **S. Fanni:** None. **P. Saba:** None. **G. Giua:** None. **P. Devoto:** None. **M. Bortolato:** None. **R. Frau:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.11/LLL43

Topic: I.05. Biomarker and Drug Discovery

Support: FAPESP 2014/20913-3
ABADHS - SP

Title: Plasma levels of metabolites differentiate first episode psychosis in schizophrenia and bipolar disorders patients

Authors: *A. C. COSTA[1], H. P. G. JOAQUIM[3], L. L. TALIB[2], W. F. GATTAZ[2]
[1]Lab. of Neurosci. LIM27 - HCFMUSP, Sao Paulo, Brazil; [2]Psychiatry, Lab. of Neurosci. LIM27 - HCFMUSP, São Paulo, Brazil; [3]Psychiatry, Lab. of Neurosci. LIM-27 - HCFMUSP, São Paulo, Brazil

Abstract: Background: Schizophrenia (SCZ) and bipolar disorder (BD) are serious psychiatric disorders that affect young adults and lead to disability, psychosocial functioning impairment and premature death. These disorders share several characteristics and symptoms and the diagnosis yet is mainly clinical. It is known that the sooner they are identified, diagnosed and treated, the better the clinical prognosis. Therefore, the development of sensitive and accurate biomarkers is highly required. Lipids play an increasingly recognized role in the neuronal function and plasticity of the brain. Glycerophospholipids and molecules-like comprise 60% of the non-aqueous portion of the brain and in an even greater proportion of the dendrites and synapses. Other metabolites directly influence its functioning and remodeling, such as acylcarnitines, sphingolipids, cholesterol and other lipids. Since lipid metabolism is altered differently in neuropsychiatric diseases, alterations in the lipid profile of the membrane can allow a discrimination between subjects in first episode psychosis (FEP). Thus, our aim was to determine plasma levels of metabolites of subjects in first episode psychosis and controls and find cutoff values that differentiate each group. Methods: Plasma samples were analyzed for 55 drug-naïve patients (28 SCZ and 27 BD) and 30 controls in this study. Determining the lipid profile was performed by mass spectrometry - Flow injection analysis, using AbsoluteIDQ p180® kit (Biocrates Life Sciences). Statistical analyzes were performed using a classification method - Classification And Regression Tree. Results: We observed that there the combination of four metabolites are able to differentiate the diagnoses studied: PC aa C26:0, PC aa C38:4, PC aa C34:3 and C16-OH. The accuracy of the method is 87,1%. Discussion: Our results suggest that the levels of some plasma metabolites differentiate subjects in FEP in SCZ, BD and controls. The levels of these metabolites can be a potential biomarker for psychosis, as well as a diagnostic marker for SCZ and BD, aiding clinical practice. The findings from this study require further validation in BD and SCZ subjects, but suggest that the metabolome is a good tool to understand the pathophysiology of these disorders and presents potential diagnostic biomarkers for the diseases studied.

Disclosures: A.C. Costa: None. **H.P.G. Joaquim:** None. **L.L. Talib:** None. **W.F. Gattaz:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.12/LLL44

Topic: I.05. Biomarker and Drug Discovery

Support: FAPESP 2014/20913-3
ABADHS - SP

Title: Kynurenine pathway is altered in plasma of schizophrenia patients

Authors: *L. L. TALIB[1], A. C. COSTA[2], H. P. JOAQUIM[3], W. F. GATTAZ[2]
[1]Psychiatry Inst. HCFMUSP, São Paulo, Brazil; [2]Lab. of Neurosci. LIM27 - HCFMUSP, Sao Paulo, Brazil; [3]Psychiatry Intitute HCFMUSP, Lim-27, São Paulo, Brazil

Abstract: The etiology of schizophrenia is still unclear. It is well-known that pro-infammatory cytokines are higher in schizophrenia patients since the frst episode psychosis comparing to healthy controls. Infammatory downstream cascades infuence different cellular pathways, like the displacement of the tryptophan (TRP) metabolism to the production of kynurenine (KYN) instead of serotonin, which results in the generation of several neuro and immunoactive metabolites. The aim of this study was to determine TRP, KYN and IL-1β plasma levels in frst-onset schizophrenia (n = 28) and healthy controls (n = 30). The plasmatic levels of TRP and KYN were decreased in schizophrenic patients (p = 0.004 and p = 0.002, respectively), but there was no diference in the ratio of KYN/TRP (p = 0.554) or either in IL-1β (p = 0.101). Positive correlation was observed between KYN and IL-1β only in the schizophrenia group (r = 0.461, p = 0.021). And, there was also positive correlation between KYN and Positive and Negative Symptoms Scale (PANSS) (r = 0.395, p = 0.037). There is no correlation between the other analytes and other parameters of PANSS. Although our results of KYN have been diferent than expected and there was no diference in the KYN/TRP ratio, we observed a positive correlation between IL-1β and KYN, corroborating fndings that pro-infammatory agents hold up the KYN pathway.

Disclosures: L.L. Talib: None. **A.C. Costa:** None. **H.P. Joaquim:** None. **W.F. Gattaz:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.13/LLL45

Topic: I.05. Biomarker and Drug Discovery

Support: All studies are funded by Blackthorn Therapeutics.

Title: An efficient, data-driven, trans-diagnostic screen for neurobehavioral health

Authors: *Y. LIU, M. S. MELLEM, H. GONZALEZ, W. J. MARTIN, P. AHAMMAD
Blackthorn Therapeut., San Francisco, CA

Abstract: Mental health screening and diagnosis requires a time-consuming interview between patients and highly-trained specialists within a clinic. Currently available remotely-administered self-assessments tend to be based on discrete diagnostic categories that may fail to reveal trans-diagnostic behavioral changes that warrant intervention. We developed a quick, trans-diagnostic, self-administered neurobehavioral health screen, which is automatically scored by computer, to

overcome some of these barriers. Using the publicly-available Consortium for Neuropsychiatric Phenomics (CNP) dataset, we applied machine learning to build statistical models comprised of trans-diagnostic item-level questions to create a screen to classify groups of subjects as healthy or possibly having a neurobehavioral disorder. CNP consists of individuals diagnosed as healthy (n=130) or as having schizophrenia (n=50), bipolar disorder (n=49) or attention deficit and hyperactivity disorder (n=43) following administration of the Structured Clinical Interview for DSM Disorders by mental health professionals. All participants provided item-level responses to multiple self-administered mental health questionnaires. We used 10-fold cross-validation with logistic regression to classify healthy control (HC) from patients based on scores of these individual items. Using all individual items (578 total), we were able to classify subjects as "HC" or "Patient" with a mean accuracy of 79%. The ROC curve, another performance evaluation metric, had a mean area-under-the-curve (AUC) of 0.88. This model also returned a measure of feature importance from the model coefficients. Thus, in order to examine if shortening the list of questions could provide comparable classification ability, we also constructed a series of models by sequentially adding in features in order of importance (starting with the most important). We found classifier performance across different subsets of questions (1 through 578) varied on AUC from 0.8 to 0.97, and it turns out that only about 5% of the items are needed for an accuracy of 91% and 0.95 AUC. This indicates that a robust classifier can be built from a compact set of questionnaire items and more features are not necessarily better in a classifier-based screen. Notably, the top features included a disproportionate number of questions regarding personality and temperament with additional questions on impulsivity, mood, and mania. Thus, the classifier with the top 5% features could be used to rapidly screen subjects across multiple neurobehavioral disorders without rater involvement, potentially remotely and repeatedly.

Disclosures: Y. Liu: A. Employment/Salary (full or part-time):; Blackthorn Therapeutics. **M.S. Mellem:** A. Employment/Salary (full or part-time):; Blackthorn Therapeutics. **H. Gonzalez:** A. Employment/Salary (full or part-time):; Blackthorn Therapeutics. **W.J. Martin:** A. Employment/Salary (full or part-time):; Blackthorn Therapeutics. **P. Ahammad:** A. Employment/Salary (full or part-time):; Blackthorn Therapeutics.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.14/LLL46

Topic: I.05. Biomarker and Drug Discovery

Title: T-448 is a specific inhibitor of LSD1 enzyme activity that has minimal impact on LSD1-GFI1B complex through the generation of a compact formyl-FAD adduct

Authors: *R. BABA[1], S. MATSUDA[1], H. OKI[2], S. MORIMOTO[1], M. TOYOFUKU[1], S. IGAKI[2], Y. KAMADA[2], K. MATSUMIYA[2], K. TSUCHIDA[3], R. HARA[1], M. ITO[1], H. KIMURA[1]
[1]Neurosci. Drug Discovery Unit, Res., [2]Biomolecular Res. Laboratories, Res., [3]Extra Value Generation Drug Discovery Unit, Res., Takeda Pharmaceut. Co. Limited, Fujisawa, Kanagawa, Japan

Abstract: Lysine-specific demethylase 1 (LSD1) is a flavin adenine dinucleotide (FAD)-dependent amine oxidase that demethylates histone H3 lysine 4 (H3K4). H3K4 methylation is a critical regulator of gene transcription, and its dysregulation has been implicated in the pathogenesis of several neurodevelopmental diseases. Therefore, treatments which restore normal levels of H3K4 methylation may be a promising approach to treat disorders associated with epigenetic dysfunction.
LSD1 forms a complex with multiple cofactors including growth factor independent 1B transcriptional repressor (GFI1B), a critical regulator of hematopoietic differentiation, in the vicinity of FAD. Known LSD1 inhibitors that target FAD have shown *in vivo* hematological toxicities, such as thrombocytopenia, probably through disruption of the interaction between LSD1 and GFI1B and the transcriptional derepression of its target genes, including *growth factor independent 1* (*GFI1*). We have identified a novel LSD1 inhibitor, T-448, 3-((1*S*,2*R*)-2-(cyclobutylamino)cyclopropyl)-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)benzamide fumarate, which induced H3K4 methylation in primary cultured rat neurons but did not induce *GFI1* mRNA in TF-1a erythroblast cell line. As expected from the *in vitro* profile, T-448 induced H3K4 methylation in mouse brains and restored learning function in NMDA receptor-hypofunction mice, showing superior hematological safety profile.
Here, we describe the mechanisms of action underlying the lack of *GFI1* mRNA induction by T-448 through the comparative analysis of T-711, a representative LSD1 inhibitor which induces *GFI1* mRNA expression. T-711 dissociated the LSD1-GFI1B complex in TF-1a cells. In contrast, T-448 had minimal impact on the complex. In addition, T-448 pre-treatment significantly weakened the T-711-induced dissociation of LSD1-GFI1B complex, suggesting that T-711 and T-448 may share the same binding site on LSD1.
Co-crystal analysis and LC/MS analysis of LSD1 and FAD suggested that FAD-adduct generated by T-711 is bulky and has a steric hindrance with GFI1B in the binding pocket of LSD1. Interestingly, T-448 produced a reduced form of FAD with a formyl group, indicating that T-448 inactivates LSD1 enzyme activity through generating a compact formyl-FAD adduct, and the formyl-FAD adduct has minimal
impact on the interaction between LSD1 and GFI1B. These results suggest that T-448 is a specific inhibitor of LSD1 enzyme activity, and the discovery of T-448 enables the *in vivo* characterization of therapeutic effects evoked by the specific inhibition of LSD1 enzyme activity.

Disclosures: R. Baba: A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Takeda Pharmaceutical Company Limited. **S. Matsuda:** None. **H. Oki:** None. **S. Morimoto:** None. **M. Toyofuku:**

None. **S. Igaki:** None. **Y. Kamada:** None. **K. Matsumiya:** None. **K. Tsuchida:** None. **R. Hara:** None. **M. Ito:** None. **H. Kimura:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.15/LLL47

Topic: I.05. Biomarker and Drug Discovery

Title: T-448, a novel LSD1 inhibitor with superior hematological safety profile, increases histone H3K4 methylation and improves learning function in NMDA receptor-hypofunction mice

Authors: *S. MATSUDA[1], R. BABA[1], S. MORIMOTO[1], M. TOYOFUKU[1], S. IWASAKI[2], R. HIBINO[1], H. KAMADA[1], T. HIRAKAWA[1], M. IWATANI[3], K. TSUCHIDA[4], R. HARA[1], M. ITO[1], H. KIMURA[1]
[1]Neurosci. Drug Discovery Unit, Res., [2]Drug Metabolism and Pharmacokinetics Res. Laboratories, Res., [3]Biomolecular Res. Laboratories, Res., [4]Extra Value Generation Drug Discovery Unit, Res., Takeda Pharmaceut. Co. Limited, Fujisawa, Kanagawa, Japan

Abstract: Epigenetic control of gene transcription by histone H3 lysine 4 (H3K4) methylation is involved in various neural functions such as learning and memory through the regulation of synaptic plasticity. Dysregulation of H3K4 has been implicated in the pathogenesis of several psychiatric and neurological disorders. H3K4 methylation levels are regulated by lysine-specific demethylase 1 (LSD1), a flavin adenine dinucleotide (FAD)-dependent amine oxidase that demethylates H3K4. Thus, treatments which restore normal levels of H3K4 methylation by the inhibition of LSD1 activity in the brain may be a promising approach to treat central nervous system (CNS) diseases associated with epigenetic dysregulation.
Targeting FAD in the active site of LSD1 is a very promising approach to design novel LSD1 inhibitors. However, in the vicinity of FAD, LSD1 forms a complex with multiple cofactors such as growth factor independent 1B (GFI1B), a critical regulator of hematopoietic differentiation. Known LSD1 inhibitors that bind to FAD have shown hematological toxicities such as thrombocytopenia, probably through the disruption of the LSD1-GFI1B complex and the transcriptional derepression of its target genes, including *growth factor independent 1* (*GFI1*). Hematological toxicity may pose a major hurdle in the development of LSD1 inhibitors as therapeutic agents.
Here, we describe our screening strategy to discover novel LSD1 inhibitors with potent epigenetic modulation and lower risks of hematological toxicity. We set the following three criteria for the selection of lead compounds: 1) selective inhibition of the enzyme activity of

purified human recombinant LSD1, 2) increase in H3K4 methylation levels and the consequent induction of gene transcription in primary cultured rat neurons, and 3) minimal impact on the transcription of *GFI1* gene in human TF-1a erythroblast cell line. As a result, T-448, 3-((1*S*,2*R*)-2-(cyclobutylamino)cyclopropyl)-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)benzamide fumarate was identified. T-448 selectively inhibited recombinant LSD1 activity, and increased H3K4 methylation and mRNA expression levels in primary cultured rat neurons. In contrast, T-448 did not increase *GFI1* mRNA expression levels in TF-1a cells. As expected from the *in vitro* profile, T-448 induced H3K4 methylation and mRNA expression levels in mouse brains, showing improved hematological safety profile. In addition, T-448 restored learning function in NMDA receptor-hypofunction mice. T-448-type LSD1 inhibitors with an improved safety profile may provide unique therapeutic opportunities for CNS disorders associated with epigenetic dysregulation.

Disclosures: S. Matsuda: A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Takeda Pharmaceutical Company Limited. **R. Baba:** None. **S. Morimoto:** None. **M. Toyofuku:** None. **S. Iwasaki:** None. **R. Hibino:** None. **H. Kamada:** None. **T. Hirakawa:** None. **M. Iwatani:** None. **K. Tsuchida:** None. **R. Hara:** None. **M. Ito:** None. **H. Kimura:** A. Employment/Salary (full or part-time):; cTakeda Pharmaceutical Company Limited.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.16/LLL48

Topic: I.07. Data Analysis and Statistics

Support: Xpansa

Title: Inferring pkc(x) function in cns based on the extracted knowledge about protein's isoform

Authors: *R. GURINOVICH[1], Y. BUINITSKAYA[2], A. PASHUK[3], V. PUNTUS[2], A. SCERBACOV[3], Y. PETROVSKIY[3]
[1]Sci.AI, Tallinn, Estonia; [2]sci.AI, Minsk, Belarus; [3]sci.AI, Tallinn, Estonia

Abstract: There are 70k+ papers mentioning PKC proteins family across the literature. Success and reproducibility of the new experiment involving PKC(x) strongly tied to correct interpretation which isoform was meant in prior scientific reports.
Based on our upstream literature-based research of PKCs' role in pain mediating, we conclude that, in spite of the close first-sight similarity, even "small" differences between isoforms PKCγ and PKCε are linked to different and unique functional roles in similar chronic and acute

perceptions of pain.
We utilize machine reasoning methods to discover possible models of biological processes and report clear feasibility to distinguish functional roles of particular PKC isoforms based on machine parsing, interlinking, and clustering of the related interactions.

Disclosures: R. Gurinovich: None. **Y. Buinitskaya:** None. **A. Pashuk:** None. **V. Puntus:** None. **A. Scerbacov:** None. **Y. Petrovskiy:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.17/LLL49

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: KAKENHI JP24111547
KAKENHI JP26460388
KAKENHI JP16KT0134C1

Title: Imaging mass spectrometry revealed the alteration of amine neurotransmitters in Scrapper-knockout mice brain

Authors: F. ETO[1,2], T. MATSUDA[1], M. SETOU[3,4], *I. YAO[1,4]
[1]Dept. of Optical Imaging, Inst. for Med. Photonics Res., [2]Dept. of Cell. and Mol. Anat, [3]Dept. of Cell. and Mol. Anat., [4]Intl. Mass Imaging Ctr., Hamamatsu Univ. Sch. of Med., Hamamatsu, Shizuoka, Japan

Abstract: The detection of low-molecular weight components such as amino neurotransmitters by imaging mass spectrometry (IMS) has been tried and developed by some groups [1, 2]. Recently, several chemical derivatization methods have been made it possible to detect them in tissues. Neurotransmitters play important parts in the brain functions and regulate a variety of biological activities. Abnormal concentrations of neurotransmitters and consequent dysfunction are connected to various central nervous system disorders. Especially, glutamate has pivotal roles in central nervous system and is closely related to neurodegenerative disease such as Alzheimer's disease. Visualization of the amino acid and monoamine of neurotransmitters is suspected to be fundamental understanding their role in various neurophysiological phenomena in different regions of the brain. Here, we applied this technique to investigate *Scrapper*-knockout (SCR-KO) mice. SCRAPPER is a synaptic protein which we have identified as an ubiquitin E3 ligase. SCRAPPER is involved in the ubiquitination of RIM (Rab3-interacting molecule) 1, an important regulator of synaptic plasticity, and thus regulates synaptic transmissions. SCR-KO has the defect in neurotransmission via excessive secretion of neurotransmitters due to the upregulation of the release probability. IMS with on tissue

derivatization revealed that the alteration of not only glutamate but also some other amino acid neurotransmitters abundances and localization in the SCR-KO mouse brain. Intriguingly, our results indicated that the rate of changes of amino acid neurotransmitters were different depending on the region of the brain. The alteration visualized by IMS analysis would reflect the local changes of neurotransmitters caused by defects in neurotransmission in the SCR-KO mouse brain. [1] Direct targeted quantitative molecular imaging of neurotransmitters in brain tissue sections. Shariatgorji et al., Neuron 2014 [2] Imaging Mass Spectrometric Analysis of Neurotransmitters: A Review. Romero-Perez GA, Takei S, Yao I. Mass Spectrom (Tokyo) 2014 [3] SCRAPPER-dependent ubiquitination of active zone protein RIM1 regulates synaptic vesicle release. Yao et al., Cell 2007

Disclosures: F. Eto: None. **T. Matsuda:** None. **M. Setou:** None. **I. Yao:** None.

Poster

701. Biomarker and Drug Discovery: Affective Disorders and Schizophrenia

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 701.18/LLL50

Topic: C.03. Parkinson's Disease

Support: NIH/NIBIB R01 EB016101
NIH/NINDS F32 NS093897
Army Research Office W911NF-16-1-0474
Saks Kavanaugh Foundation

Title: Electrochemical recording of striatal dopamine in non-human primates performing reward-biased tasks

Authors: *H. N. SCHWERDT, L. STANWICKS, K.-I. AMEMORI, H. SHIMAZU, T. YOSHIDA, S. AMEMORI, R. LANGER, M. J. CIMA, A. M. GRAYBIEL
MIT, Cambridge, MA

Abstract: Dopamine neurochemicals govern a wide range of behaviors including those related to movement, motivation, and learning. Dysregulation of striatal dopamine causes many debilitating disorders such as Parkinson's disease and major mood disorders. Understanding the role of dopamine in the specific behaviors compromised in these disorders is critical to improve diagnostics and treatment. The objective of the present study was to investigate dopamine signaling as it relates to motivational bias and motor performance. Carbon fiber microelectrode (CFM) sensors were implanted in the striatum of two rhesus macaques (*Macaca mulatta*) to selectively measure subsecond dopamine fluctuations with fast-scan cyclic voltammetry. Methods were previously established to probe multiple sites in the striatum from chronically implanted and moveable CFM sensors over several months. We recorded dopamine

concentration changes as the monkeys performed a reward-biased visual saccade task in which saccades to targets appearing on the left or right were rewarded with a small or large amount of liquid food. Physiological parameters including pupil diameter, lick movements, and pulse were synchronously recorded in the second monkey to discriminate better cryptic behavioral states. Preliminary measurements in the first monkey showed that dopamine concentration in the ventromedial striatum increased in response to unexpected food delivery, and that dopamine concentration was higher during large reward trials in comparison to small reward trials. These results agree with previous studies that have demonstrated a correlation between dopamine in the ventral striatum and reward value. Results from multi-site recording indicated diverse dopamine activity across the dorsal striatum. Early analysis suggests changes in dopamine concentration correlate with many task events including error (i.e., premature saccadic break from target), fixation cue, target appearance, and reward delivery. Trial-to-trial fluctuations of the temporal characteristics of dopamine were also observed, the dynamics of which is under investigation. This early work described here suggests heterogeneous functions of dopamine in mediating various goal-directed behaviors. These findings have the possibility to strengthen the rationale for focal pharmacological and therapeutic strategies that can be implemented for a number of disorders in which dopamine is dysregulated in a spatially variable manner. Further investigations are needed to understand the site specific functions of dopamine in motor and mood behaviors, which could help identify new therapeutic targets.

Disclosures: H.N. Schwerdt: None. **L. Stanwicks:** None. **K. Amemori:** None. **H. Shimazu:** None. **T. Yoshida:** None. **S. Amemori:** None. **R. Langer:** None. **M.J. Cima:** None. **A.M. Graybiel:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.01/LLL51

Topic: I.06. Computation, Modeling, and Simulation

Support: Exploratory Challenge 4 on Post-K Computer

Title: Parallel computing of a spiking neural network model of layered cortical sheet consisting of multiple cortical regions with long-range connections

Authors: *J. IGARASHI[1], T. YAMAZAKI[2], H. YAMAURA[3]
[1]Head Office for Information Systems and Cybersecurity, RIKEN, Saitama, Japan; [2]The Univ. of Electro-Communications, Tokyo, Japan; [3]The Univ. of Electro-Communications, Chofu, Tokyo, Japan

Abstract: Human-scale whole-brain simulations are expected to become possible using the next generation supercomputer with a theoretical performance of exaflops, which enable to study interactions among all neurons in the brain for brain function and disease.
However, there are still difficulties in realizing the simulation in load balancing of the heterogeneous architecture of the brain and communication of increasing spike information in parallel computing.
In the current study, we investigated an efficient parallelization way that can realize human-scale whole-brain simulations on the next generation supercomputer.
We focused on layered sheet neural network because 99 % of neurons and most of the volume in the brain are included in the cortex and cerebellum that form layered sheets.
Tile partitioning algorithm is one of the candidates for layered sheet model. In the current study, we introduced a new communication method to the tile partitioning method, where spike information is communicated between tiles at intervals of the minimum signal transmission delay between the tiles. The method can reduce the frequency of communication for distant tiles.
To test the performance, we applied the method to a layered cortical sheet model developed based on experimental data of the mouse primary motor cortex. The model had five layers and 18 neuron types. The numbers of neurons and synapses per square millimeter of the cortical surface were about 23000 and 220 million, respectively. The neurons were connected using Gaussian-shape connection probability function. The model consists of 4 small regular squares of different cortical sheets that were partially connected through long-range connections.
We investigated weak scaling performance of the parallelization method using 1024-16384 compute nodes of supercomputer K. With the increase in the size of the network, the frequency of communication between distant tiles decreased drastically. The computational time did not almost increase with the increase in the size of the network, which means the parallelization method achieved excellent scaling performance.
These results suggest hat proposed parallelization method may work for human-scale whole-brain simulation on the next generation supercomputer.

Disclosures: J. Igarashi: None. **T. Yamazaki:** None. **H. Yamaura:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.02/LLL52

Topic: I.06. Computation, Modeling, and Simulation

Support: Post-K Application Development for Exploratory Challenges, MEXT

Title: Examination of the roles of basal ganglia afferents in action selection and learning by spiking neuron models

Authors: J. LIÉNARD[1], B. GIRARD[3], *K. DOYA[2]
[1]Neural Computation Unit, [2]Okinawa Inst. of Sci. and Technol., Onna, Okinawa, Japan; [3]ISIR, CNRS / Sorbonne Univ., Paris Cedex, France

Abstract: We use an integrate-and-fire neuron model of the whole basal ganglia to analyze action selection and learning mechanisms. This spiking model was derived from a mean-field model parameterized in a previous work (Liénard and Girard, 2014), which was developed as a theory-agnostic model matching to a large body of anatomical and electrophysiological constraints from the macaque monkey.
We first show that the spiking version of this model exhibits selection properties in the context of an arm-reaching task, as was the case in the previous mean-field model. A comparison to neural activity recorded in the basal ganglia of monkeys performing this task further shows that the amplitude and time courses of the modeled firing rates match the experimental data.
We then carry out a systematic assessment of the functional roles of excitatory inputs to the basal ganglia, namely, the cortico-striatal pathway (CSN), the pyramidal tract (PTN), and the thalamic inputs from centromedian/parafascicular nuclei (CM/Pf). Varying the relative strength of these inputs in a selection task shows that (a) the CSN and PTN, acting alone or together, can affect which action is selected, and (b) CM/Pf inputs can prevent selection of multiple actions by narrowing selection to the most prominent one even in the case of ambiguous cortical inputs. In this model, the cortical pathways are thus compatible to the often hypothesized role of feeding action saliences to the basal ganglia, while the thalamic pathway modulates the selection under ambiguous inputs.
We finally study reinforcement learning at the cortico-striatal synapses using dopamine-modulated spike-timing dependent plasticity (DA-STDP). The exact effect of dopamine in modulating STDP, which depends on tonic and phasic DA concentration and on the dopaminergic receptors expressed by striatal medium spiny neurons, is still uncertain. We thus test different models of DA-STDP and compare the resulting learning performance. The model allows us to test different overlap of D1 and D2 receptors in striatal medium spiny neurons and to identify the range of parameters that are functionally consistent with reinforcement learning.

Disclosures: J. Liénard: None. **B. Girard:** None. **K. Doya:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.03/LLL53

Topic: I.06. Computation, Modeling, and Simulation

Support: MEXT Post-K Exploratory Challenge #4

Title: Implementation and simulation of a cerebellar model on a tile-based general spiking neural network simulator for K supercomputer

Authors: *T. YAMAZAKI[1], H. YAMAURA[1], J. IGARASHI[2]
[1]The Univ. of Electro-Communications, Tokyo, Japan; [2]RIKEN, Saitama, Japan

Abstract: Human-scale brain network simulation is an ultimate goal of computational neuroscience. In Japan, the national flagship supercomputer K has been used for this purpose, and its successor Post-K is expected to achieve the goal. In our project entitled Post-K exploratory challenge #4, we develop a high-performance general spiking neural network simulator for Post-K. The simulator decomposes a simulated network arranged on a two-dimensional grid into a set of subnetworks on two-dimensional smaller subgrids like tiling, and performs numerical simulation of the subnetworks in parallel. Spatially nearby subnetworks or tiles communicate and exchange spikes to make the set of subnewtork simulations consistent with the entire network simulation. In this study, we implemented a spiking network model of the cerebellum that we proposed previously. Using 1,024 cores on K computer, we implemented a corticonuclear microcomplex, which is considered as a functional unit of the cerebellum. Our microcomplex model is composed of 1 billion granule cells, 1 million Golgi cells, 32,000 Purkinje cells, 32,000 molecular layer interneurons, 1,024 cerebellar nuclei, and 1,024 inferior olives. These neurons were connected based on the cerebellar anatomical data, and cell parameters were estimated from electrophysiological data. Neurons were modeled as conductance-based integrate-and-fire units. In the current version, a 6-second simulation of the spontaneous activity of the cerebellum with temporal resolution of 1 millisecond completes within 2532 seconds, indicating 422 times slower than realtime. Moreover, thanks to the tile-based decomposition of the network by the simulator, we obtained good weak-scaling property, which means that the network size can be extended as large as computational cores are available on a computer. This result suggests that when an exascale-class supercomputer is built, we could perform a simulation of a human-scale cerebellar model on the supercomputer. Currently, we are working on connecting the cerebellar model with a cerebral cortical model via a thamalus model, comprising a cerebrocerebellar communication loop model. Our preliminary results demonstrate that the cerebellar model and cerebral cortical model synchronize within the theta frequency range.

Disclosures: T. Yamazaki: None. **H. Yamaura:** None. **J. Igarashi:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.04/LLL54

Topic: I.06. Computation, Modeling, and Simulation

Title: The predictive neuron, how active dendrites enable spatiotemporal computation in the neocortex

Authors: *S. AHMAD, J. HAWKINS
Numenta, Redwood City, CA

Abstract: Pyramidal neurons receive input from thousands of synapses spread throughout dendritic branches with diverse integration properties. The majority of these synapses have negligible impact on the soma. It is therefore a mystery how pyramidal neurons integrate the input from all these synapses, and what kind of network behavior this enables in cortical tissue. It has been previously proposed that active dendrites enable neurons to recognize multiple independent patterns. In this paper we extend this idea. We propose a model where patterns detected on active basal dendrites act as predictions by slightly depolarizing the soma without generating an action potential. A single neuron can then predict its activation in hundreds of independent contexts. We show how a network of pyramidal neurons combined with fast local inhibition and branch specific plasticity mechanisms can learn complex time-based sequences and form precise predictive codes. The algorithm scales well, learns continuously and demonstrates excellent performance on real-world data. We then extend the idea to handle sensorimotor sequences. Sensory inputs can change due to external factors or they can change due to our own behavior. Interpreting behavior-generated changes requires knowledge of how the body is moving, whereas interpreting externally-generated changes relies solely on the temporal sequence of input patterns. We show that our predictive network mechanism can learn both pure external temporal sequences as well as sensorimotor sequences. When the contextual input includes information derived from efference motor copies, the cells learn sensorimotor sequences. If the contextual input consists of nearby cellular activity, the cells learn temporal sequences. Through simulation we show that a network containing both types of contextual input can automatically separate and learn sensory sequences containing a blended mixture of both types of input patterns. We discuss the relationship to experimental data and testable predictions made by the model. Given the prevalence of pyramidal neurons throughout the neocortex and the importance of prediction in inference and behavior, we propose that this form of sequence memory may be a universal property of neocortical tissue.

Disclosures: S. Ahmad: None. **J. Hawkins:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.05/LLL55

Topic: I.06. Computation, Modeling, and Simulation

Title: A mechanism for sensorimotor object recognition using cortical grid cells

Authors: *M. LEWIS, S. PURDY, S. AHMAD, J. HAWKINS
Numenta, Redwood City, CA

Abstract: The neocortex is capable of modeling complex objects through sensorimotor interaction but the neural mechanisms are poorly understood. Previously we have proposed that grid cell-like neurons exist in every cortical column. In this paper, we expand on this idea and describe a two-layer network model that uses cortical grid cells and path integration to learn and recognize objects through movement. Grid cells exhibit regular tiling over environments and are organized into modules, each with a common scale and orientation. A single module encodes position within the spatial scale of the module but is ambiguous over larger spaces. A set of modules can uniquely encode many large spaces. In our model, one layer contains several grid cell-like modules. This layer provides a location signal for each learned object such that features can be associated with a specific location in the reference frame of that object. A second layer, a sensory input layer, receives the location representation as context, and uses it to encode the sensory input in the context of a location in the object's reference frame. Projections from the input layer to the location layer invoke possible locations that are consistent with the current input. Movement of the sensor updates the locations via path integration. Projections from the location layer back to the input layer predict the next input. A series of sensations followed by movements quickly results in the unique object identity that is consistent with the series of sensations and movements. Simulations show that the model can learn thousands of objects with high noise tolerance. We characterize the convergence time for object recognition, which is dependent on the number of unique features, the number of unique locations, and the total number of objects stored in the network. We compare our model to experimental data and propose testable predictions made by the model. We discuss the relationship to cortical circuitry and suggest that the reciprocal connections between layers 4 and 6 fit the requirements of the model.

Disclosures: M. Lewis: None. **S. Purdy:** None. **S. Ahmad:** None. **J. Hawkins:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.06/LLL56

Topic: I.06. Computation, Modeling, and Simulation

Title: Grid cells in the neocortex, a framework for cortical computation

Authors: *J. HAWKINS, S. AHMAD, M. LEWIS, S. PURDY
Numenta, Inc., Redwood City, CA

Abstract: Recent evidence suggests that grid cell-like mechanisms may be present in the neocortex. In this paper we propose that cells that behave similar to grid cells exist in every cortical column and play an essential role in all cortical function. We present a theoretical framework for understanding how the neocortex operates based on cortical grid cells. Grid cells in the medial entorhinal cortex represent the location of an animal in various environments. We propose that cortical grid cells, in the lower layers of the neocortex, also represent a location. Whereas grid cells in the entorhinal cortex represent the location of one thing, the body, grid cells in the cortex simultaneously represent the location of hundreds of things. Cortical columns that receive input from different parts of the body track the location of each body part relative to external reference frames. Similarly, cortical columns that receive input from the retina track the location of visual features relative to external reference frames. Including a representation of location in each column provides a framework for understanding how the cortex learns the structure and behavior of objects ("what" regions) and how the cortex maps the space around our bodies ("where" regions). The similarity of circuitry observed in all cortical regions suggests that even high-level concepts are learned and represented in a location-based framework. Cortical grid cells suggest a new way of thinking about cortical function, one that is based on the interplay of sensory input and location processing. In this paper we describe this idea and explore some of its implications.

Disclosures: J. Hawkins: None. **S. Ahmad:** None. **M. Lewis:** None. **S. Purdy:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.07/LLL57

Topic: I.06. Computation, Modeling, and Simulation

Support: DARPA (NESD) N666001-17-C-4013

Title: Stability and dynamics in finite-size stochastic neuronal spiking networks

Authors: *D. TODOROV, W. TRUCCOLO
Dept. of Neurosci., Brown Univ., Providence, RI

Abstract: In recent years, nonlinear Hawkes processes implemented as point process generalized linear models (PPGLMs) have been proven to be a useful tool for analyzing microelectrode array recordings of neuronal ensemble spiking activity. They are also related to classical models of neuronal dynamics, but unlike ODE-based neuron models, PPGLMs can be fitted directly to the spike-time data, using standard optimization tools.
An ongoing research problem is to further the understanding of the stability and neural dynamics in both univariate and multivariate (network) data-driven PPGLMs. Our previous work in

Gerhard et al. (2017, PLoS Comp Biol), showed that often simulation of these models can be unstable, leading to non-physiologically high firing rates. Thus to make nonlinear Hawkes PPGLMs useful for long-term prediction of neuronal activity and simulation studies, it is important to understand which model features cause the firing rates to become excessively large ("runaway excitation" phenomena). Despite several existing approaches based on statistical physics-inspired methods developed for the analysis of similar systems, their performance when dealing with data-driven PPGLMs, in particular multivariate models, has not been assessed yet. Here, we compare the accuracy of several theoretical approaches for predicting the occurrence of runaway excitation in multivariate Hawkes processes. The approaches are based on the following theoretical approaches: mean field approximation, 1-loop fluctuation expansion based on stochastic path integral formulations, quasi-renewal approximation (Gerhard et al., 2017) and the regular spiking limit test (Gerhard et al., 2017). These approaches are quite different conceptually, having been introduced in different settings and having limitations in different aspects.
Based on simulation studies, we identify model features that make some approaches work much better than others. In addition, we show that, in some cases, the different approaches can complement each other. Furthermore, we demonstrate how these theoretical approaches work when applied to multivariate PPGLMs fitted to nonhuman primate cortex data. Finally, we also illustrate an algorithm for efficient simulation of arbitrary nonlinear Hawkes process networks.

Disclosures: D. Todorov: None. **W. Truccolo:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.08/LLL58

Topic: I.06. Computation, Modeling, and Simulation

Support: Johns Hopkins University/Applied Physics Laboratory Ignition Grant
Johns Hopkins University/Applied Physics Laboratory Combustion Grant

Title: Self-organized swarm control using neural principles of spatial phase coding

Authors: *G. M. HWANG[1], K. SCHULTZ[1], J. D. MONACO[2], R. W. CHALMERS[1], C. W. LAU[1], B. Y. YEH[1], K. ZHANG[2]
[1]Johns Hopkins Univ. Applied Physics Lab., Laurel, MD; [2]Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Background: Recently, Monaco *et al.*[1] discovered a new class of neuronal cells, coined “phasers,” revealing an internal timing code that can localize a rodent based on activation relative to the hippocampal theta oscillation (6—10 Hz) that occurs during locomotion.

Swarmalators[2](sw), a recently formulated mathematical model consisting of distributed agents that 'sync and swarm,' augment the spatial states of agents in the swarm with auxiliary phase states that themselves are coupled to each other in the vein of the Kuramoto oscillator model.[3] This coupling of spatial and phase states introduces novel swarming behaviors due to mobilization controlled by phase-dependent attraction/repulsion and distance-dependent synchronization. We hypothesize that bottom-up control based on neural algorithms allows flexible and adaptive execution of spatial tasks not achievable with state-of-the-art top-down decentralized control mechanisms. **Objective**: We explored mathematical analysis of phase-organized swarming behavior via the sw class of space-phase[2] dynamics coupled with inputs from phaser cell. We demonstrate how sw agents can be used to model spatial navigation tasks in simple and real-world complex environments. Our neuro-inspired algorithms were benchmarked against conventional algorithms.[4] **Methods**: We exploited the auxiliary phase states in the sw formalism to provide an interface to neural coding mechanisms based on spatial patterns of temporal coordination using phaser cell dynamics. **Results**: We demonstrated that emergent behavior of agents persisted when local kernels (linear, exponential, Gaussian) were used to disable global communication in discrete-time simulations for swarms of varying sizes (10-1,000). We demonstrated that a phase-based control field can spatially guide the evolution of a swarm and simulate bump-like control similar to hippocampal place fields. Moreover, we demonstrated swarms of agents avoiding an obstacle in a computational task similar to mammalian navigation. Finally, we developed a novel metacontroller that relinquishes sw agents from a local minimum.

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2. O'Keeffe KP, Hong H, Strogatz SH. Oscillators that sync and swarm. *Nature Communications* **8,** 1504 (2017).
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Disclosures: G.M. Hwang: None. **K. Schultz:** None. **J.D. Monaco:** None. **R.W. Chalmers:** None. **C.W. Lau:** None. **B.Y. Yeh:** None. **K. Zhang:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.09/LLL59

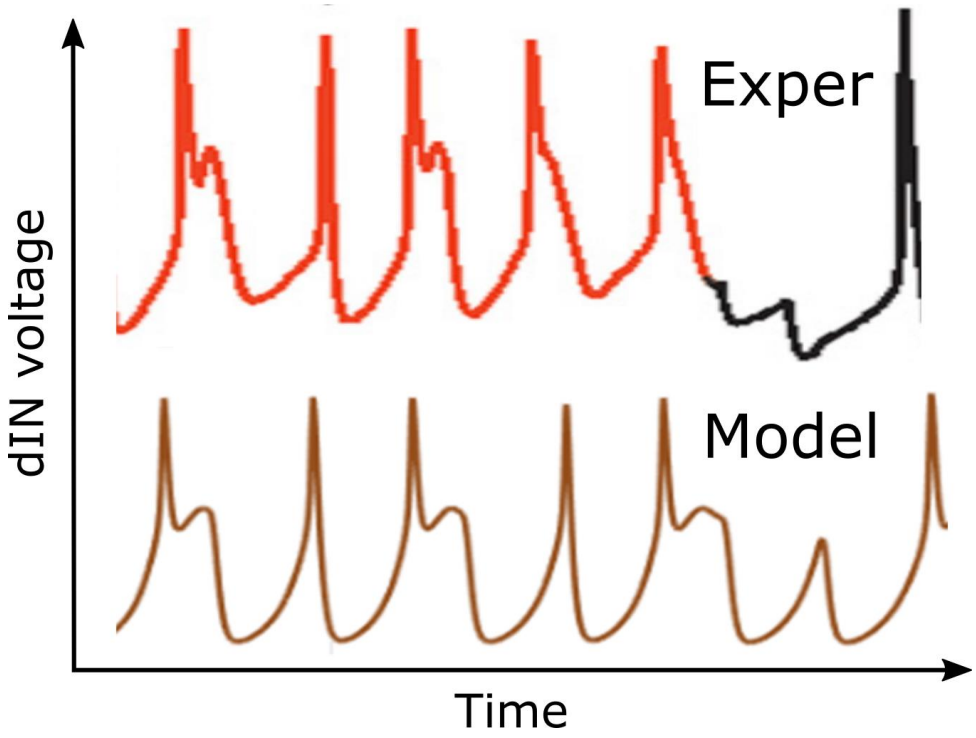
Topic: I.06. Computation, Modeling, and Simulation

Support: BBSRC grant BB/L002353/1
BBSRC grant BB/L000814/1
BBSRC grant BB/L00111X/1

Title: Swimming and synchrony in a reduced model of the xenopus tadpole central pattern generator: Bifurcations of limit cycles

Authors: *R. BORISYUK[1], A. FERRARIO[1], R. MERRISON-HORT[1,2], S. SOFFE[2,3], W. LI[3]
[1]Plymouth Univ., Plymouth, United Kingdom; [2]Univ. of Bristol, Bristol, United Kingdom; [3]Univ. of St Andrews, St Andrews, United Kingdom

Abstract: We study a minimal microcircuit controlling locomotion in two-day-old *Xenopus* tadpoles. During swimming, neurons in the spinal central pattern generator (CPG) generate antiphase oscillations between left and right half-centres. Experimental recordings show that the same CPG neurons can also generate transient bouts of in-phase oscillations between left-right centres [1].
Our aim is to understand how swimming (anti-phase) and synchrony (in-phase) oscillations can be generated by CPG neurons, find conditions for existence of these two dynamical modes, and for the existence of bi-stability. We combine a highly reduced neuronal circuit of two pairs of neurons that are known to be essential for the tadpole CPG function [2] with a detailed model of spike generation. Consideration of a small network allows us to use the bifurcation analysis for studying the dynamical modes. A biologically plausible model of spike generation allows us to mimic specific features of experimental recordings and compare the results of model simulations with experimental data.
The model produces the various outputs and for each dynamical mode the bifurcation analysis reveals the critical boundaries that separate a region of stability in the parameter space. We find a region of bi-stability where swimming and synchrony co-exit. We show that swimming is stable in a significantly larger range of parameters, and can be initiated more robustly, than synchrony. Our results can explain the appearance of synchrony bouts seen in experiments at the start of a swimming episode.
We found one more stable mode - double-period synchrony which can be observed experimentally, for example, by injecting depolarising current into a descending interneuron (dIN), or this regime can spontaneously occur during swimming. Remarkably, the spiking pattern of the double-synchrony in the reduced model perfectly reproduces this experimental finding and the shape of dIN voltages is very similar to experimental recordings (see figure). [1] Li et al. *J Neurosci*, 34: 6065-, 2014. [2] Roberts et al. *J Neurosci*, 34, 608-, 20144



Disclosures: A. Ferrario: None. **R. Merrison-Hort:** None. **S. Soffe:** None. **W. Li:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.10/LLL60

Topic: I.06. Computation, Modeling, and Simulation

Support: MINECO DPI2015-65833-P (http://www.mineco.gob.es/)
ONR MURI 14-13-1-0205 and MURI N00014-13-1-0678

Title: Rhythmic control of neural network sequential dynamics

Authors: R. LATORRE[1], *P. VARONA[1], M. I. RABINOVICH[2]
[1]Univ. Autonoma de Madrid, Madrid, Spain; [2]Univ. of California, San Diego, CA

Abstract: A large variety of experiments in neuroscience and also clinical rehabilitation protocols use rhythmic brain stimulation. In most cases the effects of this type of stimulation are only assessed in terms of global neural activations or behavioral changes. In this work we emphasize the importance of analyzing the effects of rhythmic stimulation on shaping robust sequential activity in the brain and its associated coordination. For this task, we have built a heteroclinic network of oscillatory nodes using a rate-phase model. The model is used to study

how an endogenous or external periodic frequency can control the switching among different subprocesses in a winnerless competion dynamics that shapes coherence and coordination of the network sequential activity. The analysis of this model shows that a periodic input signal in a heteroclinic motif network can effectively produce a large variety of coordinated sequential activations with key computational properties such as spectrum control, dynamical filtering and encoding enhancement. The results suggest that the analysis of sequential dynamics in protocols that use rhythmic stimulation can be used to relate neural network activity to cognitive functions, and their associated pathologies. The modeling work presented here provides insight for the design and interpretation of novel experimental paradigms with rhythmic transcranial or sensory stimulation.

Disclosures: R. Latorre: None. **P. Varona:** None. **M.I. Rabinovich:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.11/LLL61

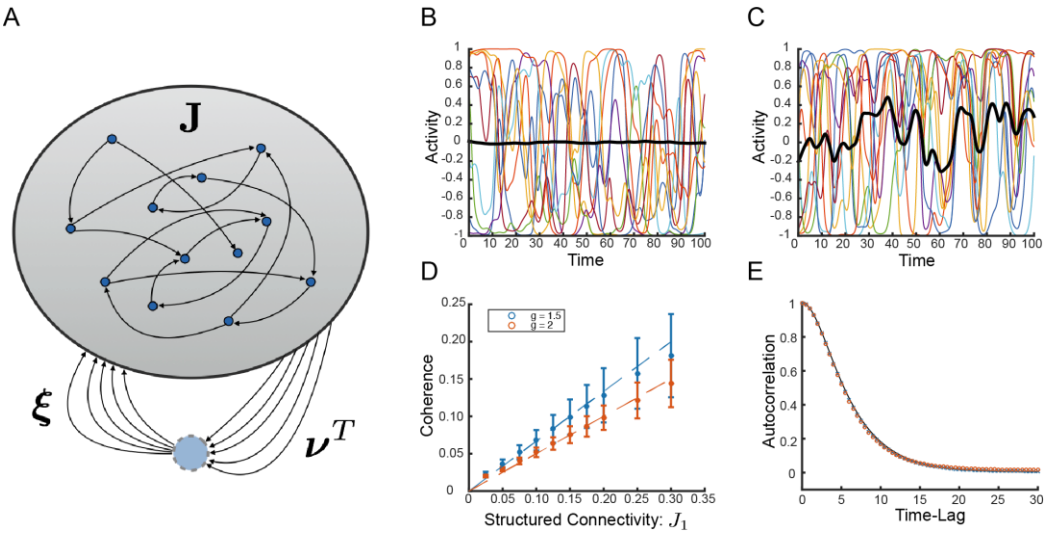
Topic: I.06. Computation, Modeling, and Simulation

Title: Coherent chaos and self-tuned criticality in a recurrent neural network

Authors: *I. D. LANDAU[1], H. SOMPOLINSKY[1,2]
[1]The Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]Ctr. for Brain Sci., Harvard Univ., Cambridge, MA

Abstract: We present a minimal model for coherent, macroscopic chaos in a recurrent neural network. We construct the model by adding a structured component to the otherwise random connectivity matrix. The structured component embeds an effectively feedforward structure via unidirectional coupling between a pair of orthogonal modes. Chaotic fluctuations propagate through the random component of the connectivity, and drive coherent activity via the structured component. The orthogonal design of the structured component ensures that feedback is not generated by the coherent activity thus allowing chaos to persevere. In a regime of small structure we apply a perturbative approach in order to solve the dynamic mean-field equations showing how coherent fluctuations initially emerge passively, driven by the chaos of independent residual local-fields. We furthermore show that this model can be generalized to yield coherent fluctuations along multiple modes of activity simultaneously. Strikingly, when we introduce a detailed balance constraint to the random component, the coupling strength of a single mode can be increased by an order of magnitude without subduing the chaotic dynamics. In this strong-structure regime the system displays fluctuations almost entirely constrained to a single coherent mode of activity with switching-like behavior reminiscent of “Up-Down” states in cortical circuits. We describe how in this regime the model achieves intermittent self-

organized criticality in which the coherent component of the dynamics self-adjusts to yield periods of slow chaos in the local fields. Furthermore we show how the dynamics depend qualitatively on the particular realization of the connectivity matrix: a complex leading eigenvalue yields coherent oscillatory behavior, while a real leading eigenvalue yields broken symmetry. Finally we examine how these phenomena scale with network-size.



Disclosures: I.D. Landau: None. **H. Sompolinsky:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.12/MMM1

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 5R01EB022717-02
Clinical and Translational Science Center (UL1TR000457) at Weill Cornell Medical College
Jerold B. Katz Foundation

Title: Simulating source localized power spectra with structural connectivity and neural mass model

Authors: *X. XIE[1], A. KUCEYESKI[2], N. D. SCHIFF[2], S. A. SHAH[2], A. RAJ[3]
[1]Dept. of Neurosci., Weill Cornell Grad. Sch. of Med. Sci., Forest Hills, NY; [2]Weill Cornell Med. Col., New York, NY; [3]Bioengineering, Univ. of California, San Francisco, San Francisco, CA

Abstract: We employ a non-linear neural mass model to simulate both locally interacting coupled neuronal populations as well as a global connectivity network to model the relationship between measureable far field electrical or magnetic potentials and the contribution of underlying neuronal connections. Using EEG and MEG recordings and their corresponding source localized functional time courses, we obtained empirical power spectra for each of the 86 gray matter regions. An optimization procedure was implemented to infer both local and global parameters of the neural mass model to reproduce the source localized spectra. We also investigated on which spatial scale does the neural mass model most accurately recapitulate the spatial distribution of power in the brain. Our simulations demonstrate that structural connectivity networks work in concert with global coupling parameters to produce modeled network brain dynamics through coupled neural masses.

Disclosures: X. Xie: None. **A. Kuceyeski:** None. **N.D. Schiff:** None. **S.A. Shah:** None. **A. Raj:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.13/MMM2

Topic: I.06. Computation, Modeling, and Simulation

Title: Combination and stability properties of echo-state recurrent neural networks

Authors: *L. KOZACHKOV[1], E. K. MILLER[2], J.-J. SLOTINE[3]
[1]MIT, Cambridge, MA, [2]Brain and Cognitive Sci., [3]Mechanical Engineering; Brain & Cognitive Sci.

Abstract: Understanding how cognitive computations are realized in massively recurrent brain circuits is a primary aim of neuroscience. In the last few years, Reservoir Computing has emerged as a promising framework for addressing this problem. Within this framework, Echo-State Networks (ESNs) have been particularly useful for capturing puzzling features of neural data in higher cortical areas, such as mixed selectivity and persistent activity. ESNs are recurrent neural networks with random—typically sparse—synaptic weight matrices and nonlinear activation functions. The dynamical richness of the RNN ensures that a linear readout from the network can be easily trained to produce desired input-output pairs.
For a network to be an ESN it must satisfy the so-called Echo-State Property (ESP), which is a mathematical condition on the synaptic weights ensuring that the system will be robust to perturbations in initial conditions. This mathematical guarantee is a useful feature of ESNs, and is not shared by other reservoir-computing approaches. However, one difficulty with ESNs is that it is not trivial to verify the ESP when multiple networks that individually satisfy this condition are connected. However, since a key feature of cortical anatomy is dense connectivity

across multiple areas, it is important to understand precisely under which connection schemes the ESP is preserved.
We show that the ESP is a special case of what is known in the dynamical systems and control literature as *contraction*. Recognizing this equivalence has several immediate consequences. Firstly, contraction analysis provides *necessary and sufficient* conditions for the verification of the ESP. Secondly, contraction analysis provides simple sufficient conditions on general, scalable connectivity schemes which preserve contraction. These guarantees pave the way for future brain modeling studies which seek to understand how information is processed not just within individual neural circuits but across *multiple* circuits, in a distributed and parallel fashion.

Disclosures: L. Kozachkov: None. **E.K. Miller:** None. **J. Slotine:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.14/MMM3

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF Grant DBI-1300426
NSF Award DMS-1412119

Title: A mathematical model for the circadian rhythmicity of pain sensitivity in the dorsal horn

Authors: *J. CRODELLE[1], S. PILTZ[2], V. BOOTH[2], M. HASTINGS HAGENAUER[3]
[1]Courant Institute, NYU, New York, NY; [2]Mathematics & Anesthesiol., [3]Univ. of Michigan, Ann Arbor, MI

Abstract: The ability of an organism to detect pain is essential for its survival. Sensitivity to painful stimuli exhibits a 24hr (circadian) rhythm, with a peak in pain sensitivity occurring in the middle of the night and a trough in mid-afternoon. In neuropathic patients, those who experience chronic pain usually accompanied by damaged or injured nerve tissue, the sensitivity of pain follows a circadian rhythm of opposite phase, with a peak in pain sensitivity occurring in mid-afternoon. Circadian rhythms underlie many biological processes, including the regulation of many immune cells that contribute to the processing of pain. Additionally, mechanisms underlying neuropathic pain remain unclear. Thus, understanding the interplay between pain processing and circadian rhythmicity is important for further understanding of pain processing. In this project, we propose possible mechanisms underlying the rhythmicity of pain sensitivity, and suggest changes in these mechanisms under neuropathic conditions that yield a rhythm of pain sensitivity that is in opposite phase. To investigate these mechanisms, we develop a firing-rate model of several populations of neurons in the dorsal horn, the main processing center of pain in the spinal cord. This model includes excitatory and inhibitory interneurons, as well as

wide-dynamic range projection neurons, whose output signals painful levels to the cortex. The input to the dorsal-horn network is modeled by Poisson spike trains generated by three types of afferent fibers, with realistic conductance velocities to reproduce the typical pain-response observed in the firing pattern of projection neurons. We validate this model by reproducing experimentally-observed phenomena such as wind-up, the increased pain response to frequency-dependent stimulation of the nociceptive (C) fibers, and pain inhibition, the decrease in pain response due to repeated stimulation of the mechanoreceptive (Aβ) fibers.
Once this model has been verified to reproduce experimentally-observed phenomena, we propose that circadian rhythmicity is introduced at the level of the afferent fibers and show that our model can capture the correct rhythmicity in pain sensitivity over a 24hr day. We then use this model to propose that the dysregulation of presynaptic inhibition could be a potential mechanism for the shift in rhythmicity of neuropathic pain sensitivity.

Disclosures: J. Crodelle: None. **S. Piltz:** None. **V. Booth:** None. **M. Hastings Hagenauer:** None.

Poster

702. Computation, Modeling, and Simulation: Network Models: Theory II

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 702.15/MMM4

Topic: I.06. Computation, Modeling, and Simulation

Support: FAPESP (Brazil) grants 2015/50122-0, 2013/07699-0 (CEPID NeuroMat), 2013/25667-8
DFG (Germany) IRTG 1740
CNPq (Brazil) Research Productivity Grant 306251/2014-0

Title: Activity patterns in networks of excitatory and inhibitory spiking neurons with synaptic noise

Authors: *A. C. ROQUE[1], R. F. O. PENA[1], M. A. ZAKS[2]
[1]Univ. de Sao Paulo, Ribeirao Preto, Brazil; [2]Humboldt-Universität zu Berlin, Berlin, Germany

Abstract: The dynamics of spontaneous population activity patterns in random networks of excitatory and inhibitory two-dimensional integrate-and-fire neurons with synaptic noise is studied. The observed activity pattern types are localized on the parameter diagram spanned by the relative inhibitory synaptic strength and the magnitude of synaptic noise. In the absence of noise, networks display transient activity, either oscillatory or asynchronous non-oscillatory, and noise generates persistent patterns. For weak noise, activity patterns are asynchronous non-oscillatory independently of synaptic strengths. For stronger noise, patterns have oscillatory and synchrony characteristics which depend on the relative inhibitory synaptic strength. In the

inhibition-dominated region of parameter space and for moderate noise magnitudes, networks disclose intermittent switches between oscillatory and low activity (quiescent) states. In the oscillatory state the neuronal voltages alternate between hyperpolarized and depolarized values in a similar fashion to up-down oscillations observed in cortical networks, and in the quiescent state they fluctuate around the resting state as low activity versions of asynchronous irregular activity modes observed in network models of integrate-and-fire neurons. Increase in noise intensity favors transitions from the quiescent to the oscillatory state and hampers the reverse transitions. The oscillatory and quiescent patterns and transitions between them are explained by using local descriptions of individual neurons in their single-neuron phase spaces combined with a phenomenological global description of the network state.

Disclosures: A.C. Roque: None. **R.F.O. Pena:** None. **M.A. Zaks:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.01/MMM5

Topic: I.07. Data Analysis and Statistics

Support: The Canadian Biomarker Integration Network in Depression (CAN-BIND)
Ontario Brain Institute (OBI)

Title: Testing a deep convolutional neural network for hippocampus automated MRI segmentation in a longitudinal sample

Authors: *N. NOGOVITSYN[1], M. MULLER[1], S. HASSEL[1], S. ARNOTT[2], A. D. DAVIS[3], G. D. HALL[5], J. HARRIS[7], M. ZAMYADI[2], R. MILEV[8], B. N. FREY[4], R. W. LAM[6], S. C. STROTHER[2], S. ROTZINGER[9], S. KENNEDY[9], G. MACQUEEN[1]
[1]Dept. of Psychiatry, Univ. of Calgary, Calgary, AB, Canada; [2]Rotman Res. Inst., Toronto, ON, Canada; [3]Dept. of Med. Physics and Applied Radiation Sci., [4]Dept. of Psychiatry and Behavioural Neurosciences, McMaster Univ., Hamilton, ON, Canada; [5]Dept. of Psychology, [6]Dept. of Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada; [7]Computing Sci., Univ. of Alberta, Edmonton, AB, Canada; [8]Dept. of Psychiatry, Queen's Univ., Kingston, ON, Canada; [9]Dept. of Psychiatry, Univ. of Toronto, Toronto, ON, Canada

Abstract: The hippocampus has been widely studied in neuroimaging research because of its critical role in the pathophysiology of psychiatric illnesses. Both automated and manual segmentation techniques are used to measure hippocampal volumes. Manual segmentation is time-consuming, expensive and vulnerable to bias in the absence of methodological controls; automated techniques may offer several advantages but their accuracy and reliability must be determined in longitudinal samples of patients. Here, we evaluated segmentation by a deep

convolutional neural network for hippocampal segmentation, hippodeep. Using a large multisite dataset, we examined the ability of hippodeep to reproduce hippocampal volumes of participants scanned across time. The Canadian Biomarker Integration Network in Depression (CAN-BIND) dataset consists of over 200 patients with major depression and 100 healthy comparison participants recruited from six sites across Canada who completed magnetic resonance imaging at three time-points (weeks 0, 2 and 8). Importantly, there was no overlap between The CAN-BIND dataset and datasets used to train and validate the algorithm. Hippodeep segmented 834 T1w brain scans from participants across all time-points. Segmentation outputs from the algorithm were stable across weeks for both healthy controls and depressed patients; Pearson's correlations were .98 to .99 for the left hippocampus of control participants compared across all weeks and .98 for the right hippocampus across weeks. Correlations were high for patients assessed across time points (.96 to .98). Hippodeep consistently produced larger volumetric measures compared to manual tracings from raters following a harmonized protocol. Visual inspection of anatomical boundaries suggested that hippodeep may have incorporated anatomical regions such as the Choroid Plexus and Fimbria in the segmentation.
These results suggest that the deep convolutional neural network hippodeep has a high test-retest reliability over time in both healthy participants and patients with major depression. Whether the relatively larger anatomic boundaries identified by hippodeep reduce the likelihood of identifying illness-associated changes in hippocampal sub-regions needs to be determined.

Disclosures: N. Nogovitsyn: None. **M. Muller:** None. **S. Hassel:** None. **S. Arnott:** None. **A.D. Davis:** None. **G.D. Hall:** None. **J. Harris:** None. **M. Zamyadi:** None. **R. Milev:** None. **B.N. Frey:** None. **R.W. Lam:** None. **S.C. Strother:** None. **S. Rotzinger:** None. **S. Kennedy:** None. **G. MacQueen:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.02/MMM6

Topic: I.07. Data Analysis and Statistics

Support: MEXT KAKENHI Grant Number 17H00764

Title: Efficient estimation of neuronal couplings from multi-point activity data: How effective is the McCulloch-Pitts model for inference?

Authors: *Y. TERADA[1,2], T. OBUCHI[2], T. ISOMURA[1], Y. KABASHIMA[2]
[1]RIKEN, Saitama, Japan; [2]Tokyo Inst. of Technol., Tokyo, Japan

Abstract: Recent advances in experimental technologies have made it possible to observe the activity levels of multiple neurons simultaneously. This provides us with much richer data than

single-neuron recording, leading to a deeper mechanistic understanding of nervous system function. A representative problem, for which such multi-point data are useful, is to identify neuronal couplings at a microscopic level. This is a very challenging problem requiring significant progress in both technological and theoretical methods.
Due to technical difficulties in treating activity from multiple neurons as continuous variables in continuous time, the standard approach for inferring neuronal couplings is to first convert the original signals to binary signals in discrete time. These binary signals can then be modeled using the McCulloch-Pitts (MP) formal neurons; indeed, numerous analytical methods have been proposed on the basis of these MP models over the course of the last decade.
However, there two unsatisfied points in the earlier studies—namely, the lack of objective criteria to determine the bin size for discretizing the signals in time and to screen significant couplings from the estimation results. The purpose of our study is to resolve these two drawbacks.
To this end, we developed two simple methods based on information theory and computational statistics. Using a property of total mutual information of the binarized data of successive times, which typically exhibits a single peak with respect to the bin size, we defined a measure for objectively determining the optimal size. Then, by comparison of the amplitude of the estimated couplings with those of estimates from randomized (surrogate) data, we established a method of computationally screening statistically significant couplings.
We then applied the proposed methods to neuronal data obtained from both simulations and cultured neuronal networks. We found that our method exhibits a fairly good performance in identifying relevant couplings, including the discrimination of their signs. We also stress that the required computational cost in our methods is sufficiently low, suggesting further applications to larger and more complicated networks. Our results highlight the utility of the MP neuron model in analyzing real nervous system function.

Disclosures: Y. Terada: None. **T. Obuchi:** None. **T. Isomura:** None. **Y. Kabashima:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.03/MMM7

Topic: I.07. Data Analysis and Statistics

Support: NYU Abu Dhabi Institute G1301

Title: A common cortical state underlying neuronal population coding

Authors: *Z. J. XU[1,2], X. GU[3], C. T. LI[3], D. W. MCLAUGHLIN[4], D. ZHOU[5], D. CAI[4]
[1]New York Univerisity, New York, NY; [2]New York Univ. Abu Dhabi, Abu Dhabi, United Arab

Emirates; [3]Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai City, China; [4]New York Univ., New York, NY; [5]Shanghai Jiao Tong Univ., Shanghai, China

Abstract: Abstract To understand how large scale neuronal networks function, it is important to identify their common dynamical operating points or states. The probabilistic characteristics of these operating states will underlie network functions such as its coding schemes. Here, directly from multi-electrode data from three separate experiments, we quantitatively identify a cortical operating state (the "probability polling" or "p-polling"), common across different species (mouse and monkey) and different behaviors. Regarding this state's functional impact, in the three experiments we confirm that it provides a framework that explains why low-order maximum entropy distribution accurately represents the distribution of neuronal firing patterns. Our simulations show that the "balanced state", common in large networks, is also a p-polling state; and that the p-polling state is closely related to weakly correlated networks. However, the p-polling state is more general than these two concepts. These results provide evidence for the p-polling state's commonality and its potential importance for neuronal coding.

Disclosures: Z.J. Xu: None. **X. Gu:** None. **C.T. Li:** None. **D.W. McLaughlin:** None. **D. Zhou:** None. **D. Cai:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.04/MMM8

Topic: I.07. Data Analysis and Statistics

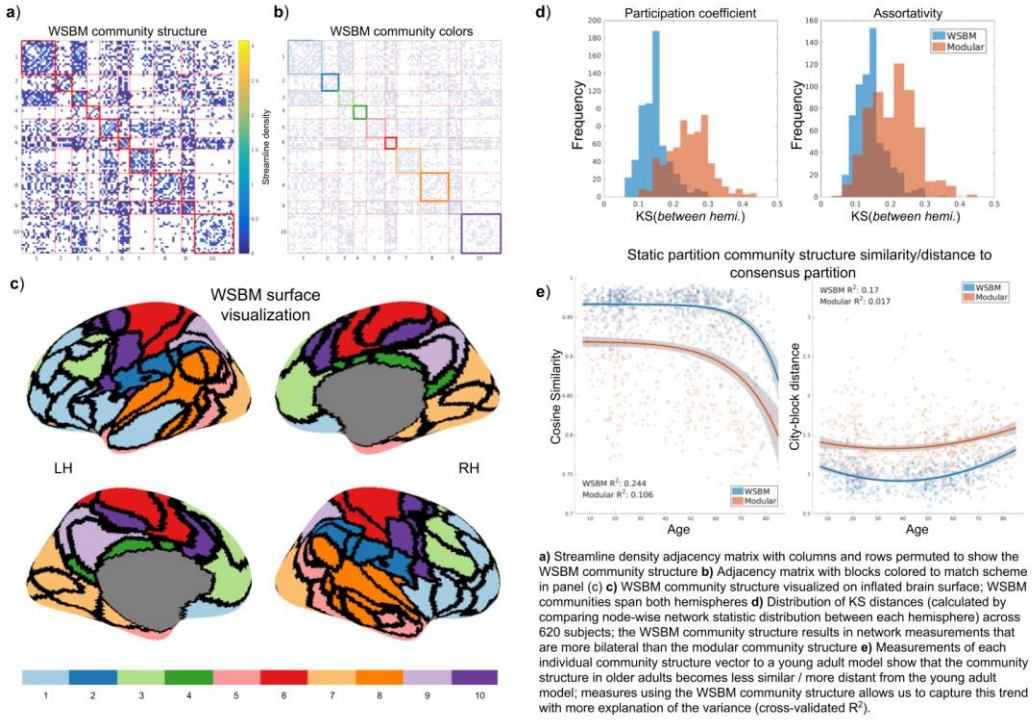
Support: NIH Grant R01 AT009036-01
NSF 1342962

Title: Weighted stochastic blockmodels of the human connectome across the life span

Authors: *J. FASKOWITZ[1], X. YAN[2], X.-N. ZUO[3], O. SPORNS[1]
[1]Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [2]Indiana Univ. Network Sci. Inst., Bloomington, IN; [3]Inst. of Psychology, Chinese Acad. of Sci., Beijing, China

Abstract: The human brain forms a complex network of anatomically interconnected neurons and brain regions, the connectome that can be modeled and analyzed with the tools of network science and graph theory. A hallmark of complex networks, including the human connectome, is the presence of subnetworks, also called communities or modules. However, uncovering network communities is an ill-defined problem with no singular solution. In this study, we employ the weighted stochastic block modeling (WSBM) framework to identify brain network communities that do not have to be exclusively modular. This generative model can identify a wide array of

community topologies, such as core-periphery and disassortative structure. Such flexibility is helpful when applied to brain networks, which might be comprised of a mixture of community structure topologies. In this project we apply the WSBM to analyze, cross-sectionally, how structural brain networks (tractography), and the community structure of these networks, are modulated across the human life span (8-85 years old, +/- 20.88; 63% F). We use the WSBM to identify a non-modular community structure model from young adult data (53 subjects; 25-35 years old; 51% female) and then analyze how the connectivity between communities of this model changes as a function of age. We identify several network blocks that exhibit significant linear and non-linear changes across age, with the most significant changes involving subregions of prefrontal cortex. Additionally, we find that WSBM communities exhibit greater hemispheric symmetry and are spatially less compact than those derived from modularity maximization. Overall, we show that the WSBM generative modeling approach can be an effective tool for describing types of community structure in brain networks that go beyond simple modularity.



a) Streamline density adjacency matrix with columns and rows permuted to show the WSBM community structure **b)** Adjacency matrix with blocks colored to match scheme in panel (c) **c)** WSBM community structure visualized on inflated brain surface; WSBM communities span both hemispheres **d)** Distribution of KS distances (calculated by comparing node-wise network statistic distribution between each hemisphere) across 620 subjects; the WSBM community structure results in network measurements that are more bilateral than the modular community structure **e)** Measurements of each individual community structure vector to a young adult model show that the community structure in older adults becomes less similar / more distant from the young adult model; measures using the WSBM community structure allows us to capture this trend with more explanation of the variance (cross-validated R^2).

Disclosures: J. Faskowitz: None. **X. Yan:** None. **X. Zuo:** None. **O. Sporns:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.05/MMM9

Topic: I.07. Data Analysis and Statistics

Support: Research supported by the European Commission through the European Joint Doctorate 'Complex oscillatory systems: Modeling and Analysis (COSMOS)', project 642563.

Title: Which spike train distance is most suitable for distinguishing rate and temporal coding?

Authors: *T. KREUZ[1], E. A. SATUVUORI[2,3,4]
[1]Inst. For Complex Systems, Sesto Fiorentino, Italy; [2]Univ. of Florence, Sesto Fiorentino, Italy; [3]Cnr, Inst. for Complex Systems, Sesto Fiorentino, Italy; [4]Vrije Univ. Amsterdam, Amsterdam Movement Sci. (AMS), Inst. for Brain and Behaviour Amsterdam (iBBA), Fac. of Behavioural and Movement Sciences, Dept. of Human Movement Sci., Amsterdam, Netherlands

Abstract: Introduction: During the last decade spike train distances have become an essential means to characterize neural coding in a wide range of neurophysiological contexts. The underlying assumption is that repeated presentations of a stimulus to a coding neuron elicit similar responses. One common way to assess similarity are spike train distances. These can be divided into spike-resolved, such as the Victor-Purpura distance **[1]** and the van Rossum distance **[2]**, and time-resolved, e.g. the ISI-distance **[3]**, the SPIKE-distance **[4]** and the RI-SPIKE-distance **[5]**.
Methods: We use independent steady-rate Poisson processes as surrogates for spike trains with fixed rate and no timing information to address two basic questions: How does the sensitivity of the different spike train distances to temporal coding depend on the rates of the two processes and how do the distances deal with very low rates?
Results: Spike-resolved distances always contain rate information even for parameters indicating time coding. This is an issue for reasonably high rates but beneficial for very low rates. In contrast, the operational range for detecting time coding of time-resolved distances is superior at normal rates, but these measures produce artefacts at very low rates. The RI-SPIKE-distance alone is sensitive to timing information only.
Conclusion: We find that the most appropriate measure depends on the rates of the data being analysed. These results are summarized in one table that allows an easy selection of the preferred measure for any kind of data **[6]**.
Software: ISI-distance **[3]**, SPIKE-distance **[4]** and SPIKE-Synchronization **[7]** as well as the directional measure SPIKE-Order **[8]** are implemented in the Matlab-based graphical user interface SPIKY **[7]**, the Matlab command line library cSPIKE, and the Python library PySpike **[9] [10]**.
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[6] Satuvuori E, Kreuz T. *J Neurosci Methods* **299**, 22 (2018)

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[8] Kreuz T, Satuvuori E, Pofahl M, Mulansky M. *New J Phys* **19**, 043028 (2017)
[9] Mulansky M, Kreuz T. Software X **5**, 183 (2016)
[10] http://www.fi.isc.cnr.it/users/thomas.kreuz/Source-Code/SPIKY.html;
http://www.fi.isc.cnr.it/users/thomas.kreuz/Source-Code/cSPIKE.html;
https://github.com/mariomulansky/PySpike

Disclosures: T. Kreuz: None. **E.A. Satuvuori:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.06/MMM10

Topic: I.07. Data Analysis and Statistics

Support: NIH R25N065723

Title: DeepBehavior: A deep learning toolbox for automated analysis of animal and human behavior imaging data

Authors: *A. ARAC[1], P. ZHAO[2], S. CARMICHAEL[3], P. GOLSHANI[4]
[1]Neurol., [2]UCLA, Los Angeles, CA; [3]UCLA Sch. Med., Los Angeles, CA; [4]UCLA Dept. of Neurol., Los Angeles, CA

Abstract: A major goal in neuroscience is to understand the relationship between brain and behavior. This can be achieved only if both brain and behavior can be defined in detail. While tremendously exciting tools exist to characterize the structure of, and the functional activity in the brain, the tools to define behavior are scarce, thus making behavior analysis very challenging. The best and the least invasive way to define a behavior is observation which can be achieved by high-speed video recording. However, analyzing these videos can be challenging and has traditionally been done manually. Here, we present a deep learning toolbox to analyze videos for detection and tracking of different body parts in mice and in humans during different behavior tasks. We achieve this by using convolutional neural networks and transfer learning approach. In particular, we present use of four different network architectures, and show examples of four different behavior paradigms. By using this technique, during a skilled food pellet reaching task in mice, paw of the mouse can be detected and 3D trajectories of the paws and the kinematic data can be obtained. Moreover, the shape and position of the paw can be determined by unsupervised learning methods using convolutional neural networks to capture the structure in the images. In social behavior tasks in mice such as three chamber test and resident intruder assay, different body parts can be tracked in multiple animals in the same cage, and their interactions can be defined accordingly. In humans, when the subjects are performing a reaching

task, individual joint movements including the digits can be tracked simultaneously. This provides a very detailed, and rich dataset for behavior analysis. Of note, for any of these videos, there is no need to place a marker or tag the body parts before video recordings, thus allowing a more natural observation and analysis of the behavior. By using automated and unbiased methods based on deep learning techniques, behavior analysis can be performed at an unprecedented detail and speed.

Disclosures: A. Arac: None. **P. Zhao:** None. **S. Carmichael:** None. **P. Golshani:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.07/MMM11

Topic: I.07. Data Analysis and Statistics

Support: ERC grant 682426 — VISONby3DSTIM

Title: Multi-day, stable, functional neuronal network measurement in three dimensions from a depth exceeding 1mm

Authors: *A. PLAUSKA[1], G. SZALAY[1], M. MAROSI[1], T. TOMPA[1], D. P. PINKE[1], G. HORVÁTH[1], D. NAGY[1], C. CSUPERNYÁK[1], B. HEIZER[1], L. JUDÁK[1], P. MAÁK[2], M. VERESS[2], A. FEHÉR[2], G. KATONA[3], B. RÓZSA[1,3]
[1]Lab. of 3D Functional Network and Dendritic Imaging, Inst. of Exptl. Medicine, HAS, Budapest, Hungary; [2]Dept. of Atomic Physics, Budapest Univ. of Technol. and Econ., Budapest, Hungary; [3]The Fac. of Information Technol., Pázmány Péter Catholic Univ., Budapest, Hungary

Abstract: Functional two-photon imaging is an essential tool in understanding connectivity and operation of neural networks in the brain. Achieving this goal requires gaining access to deeper layers than the superficial ones. Ideally, functional cortical imaging should gather data from all the cortical layers in the area of interest. Understandably, recording from large population of neurons results in hundreds of thousands traces and calls for automatization of analysis to extract data from recordings.
Here we report results of a fast deep imaging in mouse visual cortex area V1, encompassing all 6 layers in it. The latest generation of our three-dimensional acousto-optical microscope makes it possible to measure up to 1000 cells from an 800 x 800 µm field of view as deep as 1000 µm under the pia, while maintaining 20-40 Hz temporal resolution for functional imaging of neurons. The imaging was performed on transgenic adult mice of either sex. The same population was imaged for multiple number of repetitions over the span of several days, yielding a large amount of data (tens of Gigabytes) for one animal. Due to time consuming preparation for the measurement and the measurement duration itself one has to consider utilizing automated

data analysis methods for an efficient data extraction. In this research different sections of the workflow are performed by separated personnel with manual interception and criteria set between each session. However, one has to be aware of an increased possibility for errors or missed findings due to the overly intense automation.
We have developed a complex, semi-automatic workflow for three-dimensional acousto-optical measurements and analysis, involving preparation of the animals, repeated measurements for multi-day imaging session from the same set of neurons, also involving data analysis and visualization. Our analysis software allows automatic cell detection, background and ΔF over F calculation as well as sorting and visualization of the data, while having multiple check points for human interaction minimizing the room for error.

Disclosures: A. Plauska: None. **G. Szalay:** None. **M. Marosi:** None. **T. Tompa:** None. **D.P. Pinke:** None. **G. Horváth:** None. **D. Nagy:** None. **C. Csupernyák:** None. **B. Heizer:** None. **L. Judák:** None. **P. Maák:** None. **M. Veress:** None. **A. Fehér:** None. **G. Katona:** None. **B. Rózsa:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.08/MMM12

Topic: I.07. Data Analysis and Statistics

Support: JSPS KAKENHI Grant Number 16KT0134
MEXT KAKENHI Grant Number 25120011

Title: A manifold learning approach to imaging mass spectrometry analysis in mice brain

Authors: *H. SUETANI[1,2], F. ETO[3,4], I. YAO[3,5]
[1]Oita Univ., Oita, Japan; [2]Riken Ctr. for Brain Science, RIKEN, Wako, Japan; [3]Dept. of Optical Imaging, Inst. for Med. Photonics Res., [4]Dept. of Cell. and Mol. Anat, [5]Intl. Mass Imaging Ctr., Hamamatsu Univ. Sch. of Med., Hamamatsu, Shizuoka, Japan

Abstract: Recently, the methods of imaging mass spectrometry (IMS)[1], which is the combinations of mass spectrometry that ionizes chemical species and sorts the ions based on their mass-to-charge ratio with spatial visualizations, are receiving attention in the various fields of science and technology.When the IMS is applied to a sample such as biological tissues, for each spatial point , the information on particles and molecules is obtained as the ion signals as a function of the mass-to-charge ratio called the mass spectrum. Therefore, data in association with IMS is composed of a huge number of mass spectra, which brings difficulty to apply conventional statistical analyses.In this study, we propose an approach based on “manifold learning”[2], which is a framework of unsupervised nonlinear dimensionality reduction for

visualizing high-dimensional data into a low-dimensional space for analyzing the IMS data. To this end, we first introduce a distance measure that is based on the information geometry[3] for measuring the similarity between two mass spectra in an appropriate way. Then, we employ conventional algorithms of manifold learning including the LLE, the ISOMAP, and the t-SNE using the information-geometrical distance measure.We apply our approach to slices of the mouse brains and show that our prosed approach is useful for visualizing a set of the mass spectra as well-separated “islands” of points where each island reflects a specific character of chemical species in the brain.We also discuss how our results can be interpreted in terms of neurophysiology.
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Disclosures: H. Suetani: None. **F. Eto:** None. **I. Yao:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.09/MMM13

Topic: I.07. Data Analysis and Statistics

Title: Large-scale automated deep neural network training framework for robust inference of neural ensemble dynamics

Authors: *M. R. KESHTKARAN[1], C. PANDARINATH[1,2]
[1]Coulter Dept. of Biomed. Engin., Emory Univ. / Georgia Tech., Atlanta, GA; [2]Dept. of Neurosurg., Emory Univ., Atlanta, GA

Abstract: Over the past decade, the ability to record from large populations of neurons has increased exponentially. These capabilities motivate powerful new tools to understand the computations underlying the activity of large neural ensembles. We recently demonstrated a deep learning tool, Latent Factor Analysis via Dynamical Systems (LFADS), that uses sequential autoencoders (SAEs) to precisely estimate neural ensemble dynamics on a single trial, moment-by-moment basis (Pandarinath et al. 2017, BioRxiv). In the motor cortex (M1), for example, estimating ensemble dynamics led to a dramatic increase in our ability to decode arm movements during reaching. However, like many deep learning methods, SAEs require careful hand-tuning of complex model hyperparameters (HPs) to ensure optimal performance, which is challenging, time-consuming, and critically limits their application. Importantly, current SAEs are susceptible to overfitting if HPs are automatically searched, due to a lack of appropriate cross-validation strategy. We addressed this by developing a new cross-validation strategy that allows the SAE to

be trained on partially-sampled time-series data, and validated on the complementary samples. Further, we developed a novel network optimization scheme to force the SAE to only model structure that is shared across neurons, which helps avoid overfitting. With these modifications in place, we created a large-scale, automated HP tuning framework based on Population Based Training (PBT; Jaderberg et al. 2017, arXiv), which uses distributed computing to train many tens of models simultaneously while using evolutionary algorithms to tune HPs and find optimal models. We tested the modified SAE along with PBT on M1 ensemble activity from two monkeys performing a center-out task, and found that it consistently matched or outperformed the performance of the original LFADS with hand-tuned HPs (arm movement decoding, quantified by R^2). Strikingly, the modified SAE with PBT was more robust to dataset size, achieving ~30% better R^2 than LFADS for limited datasets. Finally, the modified SAE with PBT learned models with better generalization to movement conditions they had not been trained on: when more than half of the conditions were held out during model training, but used in decoding, the modified SAE with PBT led to an ~11% improvement in R^2 over LFADS. Our large-scale, automated training framework for SAEs will provide the neuroscience community with a robust and easy to use tool to estimate neural ensemble dynamics. We aim to make this tool applicable to many different regions of the brain, to further scientific study of how neural ensembles perform computation.

Disclosures: M.R. Keshtkaran: None. **C. Pandarinath:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.10/MMM14

Topic: I.07. Data Analysis and Statistics

Support: Dept of Energy Computational Science Graduate Fellowship
NIH NRSA 1F31NS089376-01
Burroughs Wellcome Foundation
Sloan Foundation
Simons Foundation
Office of Naval Research
McKnight Foundation

Title: Automatic alignment of neural data by piecewise linear time warping

Authors: *A. H. WILLIAMS[1], B. POOLE[1], N. MAHESWARANATHAN[1], A. K. DHAWALE[2], D. H. BRANN[2], B. OLVECZKY[3], E. TRAUTMANN[1], T. FISHER[1], S. RYU[4], K. V. SHENOY[5], R. SHUSTERMAN[6], C. D. WILSON[7], D. RINBERG[7], S. GANGULI[1]
[1]Stanford Univ., Stanford, CA; [3]OEB, [2]Harvard Univ., Cambridge, MA; [4]Palo Alto Med. Fndn.,

Palo Alto, CA; [5]EE, BioE & Neurobio., Howard Hughes Med. Inst. - Stanford Univers, Stanford, CA; [6]Univ. of Oregon, Eugene, OR; [7]New York Univ., New York, NY

Abstract: Differences in attentional state, biophysical kinetics, and other unobserved latent variables often cause neural firing patterns to be shifted and skewed in time across repeated behavioral trials. In the rodent olfactory bulb, mitral cell activity is highly stochastic when aligned to odor presentation, but aligning to inhalation reveals precise temporal coding [1, 2]. In motor tasks, the onset and duration of movements may vary considerably from trial-to-trial, even for relatively simple behaviors.

To account for variability in timing, studies have manually warped neural activity to align with sensory cues or behavioral events (e.g., [3]). However, even simple experiments are often compatible with multiple alignment strategies, and neural activity measured far from the sensory/motor periphery may not have reliable behavioral or sensory correlates. Ideally, the optimal temporal alignment for each trial could be directly inferred from the neural activity alone. Building off of previous work [4, 5, 6] we propose an unbiased and data-driven method to achieve this aim. We simplify previous approaches by considering piecewise linear time warpings, which are both simpler to interpret and more easily scaled to larger datasets. We apply this method to datasets derived from diverse brain regions (olfactory bulb, motor cortex, and orbitofrontal cortex) and animal models (rodent and primate).

Despite its simplicity, the model can uncover strong effects that transfer to measurable behaviors and held out neural data. In primate hand reaching, applying time warping to hand velocity traces reduces the variance in reaction times by ~80% when the model is fit purely on neural data. In rat motor cortex, we uncover prominent oscillations in firing rate that are imperceptible in single-trial data and are obscured by naive trial-averaging. For this dataset, time warping increases the signal-to-noise ratio by two- to four-fold in neurons that are held out during model fitting. Overall, this method identifies previously hidden but surprisingly precise and behaviorally relevant spike timing patterns, enabling the discovery of new circuit functions and mechanisms.
[1] Shusterman et al. (2011). Nature Neurosci, 14:1039-[2] Shusterman et al. (2017). bioRxiv, 174417[3] Kobak et al. (2016). eLife, 5:e10989[4] Poole et al. (2017). COSYNE, III-14[5] Lawlor et al. (2018). bioRxiv, 194498[6] Duncker et al. (2018). COSYNE, II-87

Disclosures: A.H. Williams: None. **B. Poole:** None. **N. Maheswaranathan:** None. **A.K. Dhawale:** None. **D.H. Brann:** None. **B. Olveczky:** None. **E. Trautmann:** None. **T. Fisher:** None. **S. Ryu:** None. **K.V. Shenoy:** None. **R. Shusterman:** None. **C.D. Wilson:** None. **D. Rinberg:** None. **S. Ganguli:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.11/MMM15

Topic: I.07. Data Analysis and Statistics

Support: 2016R1A2B3016609
NRF-2014M3C7A1046042

Title: Prediction of amyloid PET positivity from multi-modal magnetic resonance imaging using deep learning

Authors: *S. BANG[1], Y.-H. PARK[1], M. BYUN[2], D. YI[2], J. LEE[3], Y. LEE[4], Y. KIM[6], K. KANG[5], C.-H. SOHN[5], D. LEE[7], J.-M. LEE[1]
[1]Dept. of Biomed. Engin., Hanyang Univ., Seoul, Korea, Republic of; [2]Inst. of Human Behavioral Medicine, Med. Res. Ctr. Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Biomed. Res. Institute, Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of; [4]Dept. of Neuropsychiatry, [5]Dept. of Radiology, Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of; [6]Dept. of Nuclear Med., SMG-SNU Boramae Med. Ctr., Seoul, Korea, Republic of; [7]Dept. of Psychiatry, Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Alzheimer's disease (AD) is the most common type of dementia, which is considered to be important along with the emergence of a population aging society. Despite of recent advances in amyloid PET imaging to measure beta-amyloid (Aβ) deposition in living human brain, which is one of the hallmark of AD pathologies, the use of amyloid PET is still limited due to its high costs and low accessibility. In this context, prediction of individual's cerebral Aβ deposition using magnetic resonance imaging (MRI) can have several strengths including lower expenses, higher accessibility, and no radiation exposure. Recently, the development of deep learning has made it possible to obtain complementary information from images of different modalities. Here, we propose the modified model of the conventional Convolutional Neural Network (CNN) structures to predict Aβ positivity using multi-modal magnetic resonance (MR) image data of old-aged individuals. As a predictor of this model, multi-modal MR image data including T1, T2, and FLAIR of cognitively impaired (CI) older adults consisting of mild cognitive impairment (MCI) and AD dementia groups were obtained from the database of Korean Brain Aging Study of the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), an ongoing prospective cohort study started in 2014. All participants in the KBASE cohort underwent comprehensive clinical assessment, multi-modal MRI scans, and [^{11}C]PiB PET. As an outcome of this prediction model, amyloid PET positivity for each subject, defined by quantitative measurement of PiB uptake on PET image was used. After pre-processing MR images and quality control, MR images of 476 individuals were used for development and testing of deep learning based prediction model. Accuracy of model was measured by area under the curve (AUC) value.

Table 1

Performance metrics	AD dementia	MCI	Cognitively impaired
AUC	90.24%	86.08%	87.70%

In Table 1, we provided a quantitative evaluation on our dataset. Our method produces high accuracies and few false negative errors. In this work, we showed the possibility of predicting the positivity of amyloid beta with MRI data only.

Disclosures: S. Bang: None. **Y. Park:** None. **M. Byun:** None. **D. Yi:** None. **J. Lee:** None. **Y. Lee:** None. **Y. Kim:** None. **K. Kang:** None. **C. Sohn:** None. **D. Lee:** None. **J. Lee:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.12/MMM16

Topic: I.07. Data Analysis and Statistics

Support: G1301
NSFC-11671259
NSFC-91630208
NSFC-11722107
NSF DMS-1009575
NSFC-31571071

Title: Spike-triggered regression (STR) method for neuronal network reconstruction

Authors: *Y. ZHANG[1,2], Y. XIAO[1,2], D. ZHOU[3], D. CAI[2,1,3]
[1]New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates; [2]New York Univ., New York, NY; [3]Shanghai Jiao Tong Univ., Shanghai, China

Abstract: Neurons in our brain are connected with one another to process information. The single neuron behavior has been well characterized, however, the connectivity of a large group of neurons is poorly understood. Based on the feasibility of recordings of intracellular membrane potentials and spikes of neuronal network dynamics, we propose the spike-triggered regression (STR) method, which can efficiently recover the underlying network structure even under the conditions that recording time is relatively short (20~100s) or network dynamics is nearly synchronous. In particular, pairwise application of STR can accurately predict the coupling strength between any pairs of neurons in sparse networks. Our work provides a potential means of shedding light on the organization of the neuronal network in the brain.

Disclosures: Y. Zhang: None. **Y. Xiao:** None. **D. Zhou:** None. **D. Cai:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.13/MMM17

Topic: I.07. Data Analysis and Statistics

Title: Supervised dimensionality reduction on spike trains with smooth-constrained autoencoder

Authors: *Y. WU[1], A. A. FAISAL[2]
[1]Imperial Col. London, London, United Kingdom; [2]Imperial Col. London, London, United Kingdom

Abstract: Neural recordings with multiple electrodes enable researchers to study activities of neural populations simultaneously, in order to capture features only appear in population level. Dimensionality reduction methods are commonly applied for feature extraction from multi-dimensional spike trains. We propose here a supervised dimensionality reduction method using a time-convolutional autoencoder, which is capable of finding a latent space best representing task-relevant features. Since spike trains are binary, stochastic and could be extremely sparse, it is not feasible to apply vanilla autoencoder without any constraints or approximations. Thus, we introduce smooth constraints to convolutional kernels to reduce the number of free parameters and at the same time to project spikes to continuous latent space. Smooth parameters are assigned as attributes of individual neurons in the population and are trained together with the autoencoder. The entire structure of our neural network consists of three components: 1. an encoder performing both smoothing and projection; 2. a decoder reconstructing signals from latent space; 3. a predictor providing task-dependent supervised information. The loss function is defined as a combination of both reconstruction loss and prediction loss and the network is trained with back-propagation. Our model is able to implement either supervised (with predictor) or unsupervised (without predictor) dimensionality reduction. It also shows advantage: 1. 1-step optimisation, no need to apply smooth pre-processing procedure compared with conventional 2-step methods; 2. analytical solution, achieving results directly via analytical calculation instead of optimisation (compared with Gaussian process methods); 3. task-relevant features, supervised information can be easily introduced to our model without changing the structure or training algorithm.

Disclosures: Y. Wu: None. **A.A. Faisal:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.14/MMM18

Topic: I.07. Data Analysis and Statistics

Support: This research was supported by a grant(18CTAP-C129722-02) from Technology Advancement Research Program (TARP) funded by Ministry of Land, Infrastructure and Transport of Korean government.

Title: Driving fatigue detection by brain activity estimated from electrodermal activity

Authors: *P. SEO, D. YEO, H. KIM, S. HER, S. CHOI, K. KIM
Biomed. Engin., Yonsei Univ., Wonju-Si, Gangwon-Do, Korea, Republic of

Abstract: This study is to develop core technologies for a practical bio signal-based driving assistance system, which exploits the physiological signals from a wrist-type sensor module that can replace the electroencephalogram (EEG) information. We tried to recognize driver's fatigue status based on the EEG biomarkers estimated from electrodermal activity (EDA)Twenty-one healthy, driver license holding university students participated in the experiment. Every participant slept enough the night before driving, and they had routine daytime. Taking Cold medicine, alcohol, and caffeine was inhibited before driving. Multichannel EEGs, EDA, and driver's face video were recorded for 90 minutes monotonous driving on PC based driving simulator, from 8 p.m.Driver's fatigue was descripted by scoring driver's face video by four experimenters in every 1 minute, based on Karolinska Sleepiness Scale (KSS). We decided KSS score over 6 as fatigue state, and under 5 as awaken state. The EEG spectrum power was calculated using short-time Fourier transform (STFT) with a 50% overlapped hamming window of 10 seconds was applied. We selected channel-averaged alpha-band spectrum power in every 1 minute, which is the most correlated with KSS score as a training feature of support vector machine (SVM) classifier. We used support vector regression (SVR) to estimate the input feature of SVM above, from mean EDA amplitude in every 1 minute. Finally, we combined regression model (EDA to EEG) and classifier (EEG to KSS).We calculated intra-subject classification accuracy. The classification accuracy was 59.52 ± 13.06%, maximum 82.60%. Sensitivity and specificity were 62.80 % and 56.25%. Although we did not use the best feature to classification in this paper, with selecting optimal features it could be useful.

Disclosures: P. Seo: None. **D. Yeo:** None. **H. Kim:** None. **S. Her:** None. **S. Choi:** None. **K. Kim:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.15/MMM19

Topic: I.07. Data Analysis and Statistics

Support: This work was supported by Institute for Information & Communications Technology Promotion (IITP) grant funded by the Korea government (No. 2017-0-00451, Development of BCI based Brain and Cognitive Computing Technology for Recognizing User's Intenti

Title: Zero shot generative adversarial network for EEG based classification

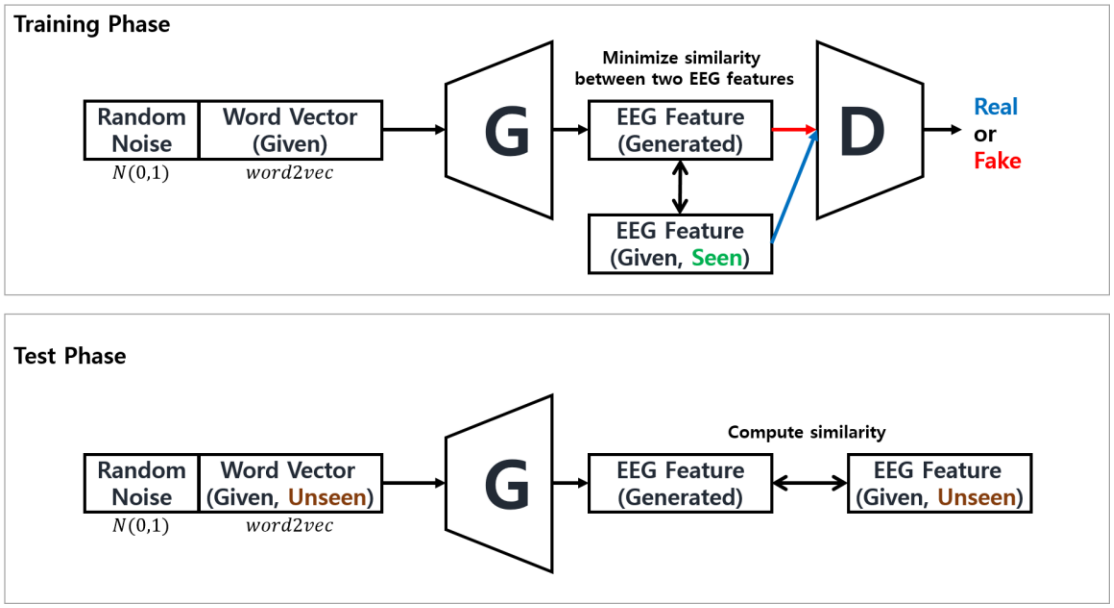
Authors: *S. HWANG[1], K. HONG[2], H. BYUN[3]
[1]CVPR Lab., [2]Yonsei Univ., Seoul, Korea, Republic of; [3]Yonsei Univ., Seou, Korea, Republic of

Abstract: Introduction: EEG-based classification has researched in several decades. However, lack of dataset for EEG-based classification is a still challenging problem. To overcome the issue, we first propose the method to classify EEG feature without training using Zero-Shot Learning(ZSL) model and Generative Adversarial Network(GAN). Method: The proposed model consists of following two-part: generative network G and discriminative network D. Given the EEG data and semantic vectors, G tries to generate EEG features using semantic vectors with random noise, while D distinguish the EEG features are real (Given) or fake (Generated). Both G and D consist of three Fully Connected (FC) layers followed by Rectified Linear Unit (ReLU) and Dropout. Experiment: We evaluate our model using the Mindbigdata (David 2018), that is recorded with the stimulus of seeing random images from ImageNet ILSVRC2013 (Zeiler et al. 2013). The dataset provides a large amount of EEG signals containing 3 seconds signals with 569 class labels. To generate EEG images by semantic vectors, we use pre-trained word2vec containing ImageNet labels while we have used MFCC for the EEG representation. Among the 569 classes, we selected 70 seen classes for training the proposed network, 30 unseen classes are used to test. We adopt Adam optimization algorithm to learn the proposed model. We found that Zero-shot GAN can recognize the unseen classes. Conclusion: We first introduce Zero-shot GAN to recognize untrained EEG dataset. Furthermore, the proposed ZSL model showed the possibility for classifying untrained EEG features.

Zero-shot Accuracy on Mindbig dataset

Channel	**Spectrum(David et al. 2018)**		**MFCC**	
	Top-1	Top-5	Top-1	Top-5
AF3	4.3	17.13	**5.71**	16.93

AF4	4.72	16.93	4.53	17.13
T7	N/A	N/A	5.51	**17.32**
T8	N/A	N/A	5.12	16.34
Pz	4.72	17.13	4.92	16.14
All Channels	4.92	15.35	5.31	15.16
We trained 70 seen classes, and 30 classes are use to test. We evaluated Zero-shot Accuracy using two types of EEG features.				



Disclosures: S. Hwang: None. **K. Hong:** None. **H. Byun:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.16/MMM20

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant DC009183
Simons Foundation Global Brain grant
NSF GRFP Fellowship
NSDEG Fellowship
DOE CSGF Fellowship

Title: Unsupervised discovery of neural sequences in large scale recordings

Authors: *A. H. BAHLE[1], E. L. MACKEVICIUS[1], A. H. WILLIAMS[2], N. I. DENISENKO[1], S. GU[1], M. S. GOLDMAN[3], M. S. FEE[1]
[1]MIT, Cambridge, MA; [2]Stanford Univ., Stanford, CA; [3]Univ. of California Davis Ctr. for Neurosci., Davis, CA

Abstract: The ability to identify interpretable, low-dimensional features that capture the dynamics of large-scale neural recordings is a major challenge in the field of neuroscience. Dynamics that include repeated temporal patterns (which we call sequences), are not succinctly captured by traditional dimensionality reduction techniques such as principal components analysis (PCA) and non-negative matrix factorization (NMF). The presence of neural sequences is commonly demonstrated using visual display of trial-averaged firing rates (1-3). However, the field suffers from a lack of task-independent, unsupervised tools for consistently identifying sequences directly from neural data, and cross-validating these sequences on held-out data. We describe an extension to an existing technique, convolutional NMF, that avoids its common failure modes. This extension, which we call seqNMF, provides a framework for extracting sequences from large high-dimensional datasets, and is easily cross-validated to assess the significance of each extracted factor. We apply seqNMF to test the recovery of sequences from ground-truth simulated datasets, and to demonstrate its performance on previously published data from rat hippocampus, as well as a new dataset from the songbird pre-motor area HVC. In the hippocampal data, seqNMF automatically identifies neural sequences that match those calculated manually by reference to behavioral events (1-2). The bird dataset was recorded in animals that never heard a tutor, and therefore sang pathologically variable songs. Despite this variable behavior, seqNMF is able to discover stereotyped neural sequences. These sequences are deployed in an overlapping and disorganized manner, strikingly different from what is seen in tutored birds. Thus, by identifying temporal structure directly from neural data, seqNMF can enable dissection of complex neural circuits with noisy or changing behavioral readouts (4).
1.) Fujisawa, S., Amarasingham, A., Harrison, M. T. & Buzsáki, G. Behavior-dependent short-term assembly dynamics in the medial prefrontal cortex. *Nature Neuroscience* **11,**823–833 (2008).
2.) Pastalkova, E., Itskov, V., Amarasingham, A. & Buzsáki, G. Internally generated cell assembly sequences in the rat hippocampus. *Science* **321,**1322–1327 (2008).
3.) Harvey, C. D., Coen, P. & Tank, D. W. Choice-specific sequences in parietal cortex during a virtual-navigation decision task. *Nature* **484,**62–68 (2012).
4.) https://github.com/FeeLab/seqNMF

Disclosures: A.H. Bahle: None. **E.L. Mackevicius:** None. **A.H. Williams:** None. **N.I. Denisenko:** None. **S. Gu:** None. **M.S. Goldman:** None. **M.S. Fee:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.17/MMM21

Topic: I.07. Data Analysis and Statistics

Title: Simulation-based evaluation of PCA application to neuronal population activity

Authors: *A. FILIPPOW[1,2], B. DANN[1], H. SCHERBERGER[1,2]
[1]German Primate Ctr., Goettingen, Germany; [2]Dept. of Biol. and Psychology, Univ. of Göttingen, Göttingen, Germany

Abstract: Simultaneous recording from large numbers of neurons has recently become available, and its analysis has revealed low-dimensional representations of task parameters within these high-dimensional neural populations. Principal component analysis (PCA), or one of its variant, is the most commonly used method for extracting the underlying low-dimensional population structure. Although PCA is deterministic, its application on neuronal activity needs to be justified and tested. Neuronal spiking activity has various limitations, e.g., it is a point process, its firing rates cannot be negative, and neural recordings are subsamples of the underlying population. We hypothesize that these properties limit the usability of PCA on neuronal population activity.
Investigating the performance of PCA on real recordings is difficult because we do not know the ground truth of the underlying low-dimensional population structure. Therefore we simulated neuronal population spiking activity with known structure. Firing rates for simulated neurons were sampled from neurons recorded from three macaque cortical grasping networks. To generate the population structure, firing rates were modulated by a set of latent variables. Contributions of single neurons to each latent variable were randomly selected and orthogonalized between latent variables at the population level. As an example, we modeled a center-outreach task by three latent variables, representing the vertical and horizontal components of the motion and a condition-independent component, respectively.
Principal components, despite capturing maximal variance, rarely captured single latent variables. Instead, they consisted of random mixtures of noise and linear combinations of latent variables. Still, PCA performed well in recovering the true number of latent variables. Furthermore, canonical correlation between the latent variables and the principal components revealed that PCA reliably captures the dynamics of the latent variables. For a larger number of latent variables, the distribution of variance captured per principal component tended towards a power law curve, regardless of the true distribution of latent variable weights.
Overall, we found PCA to be a reliable method for estimating the dimensionality of a neuronal dataset, but a different method is necessary for recovering the true latent dimensions. Notably,

the distribution of variance captured by each principal component did not represent the true distribution of latent variable weights and conclusions should therefore be drawn carefully.

Disclosures: A. Filippow: None. **B. Dann:** None. **H. Scherberger:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.18/MMM22

Topic: I.07. Data Analysis and Statistics

Support: NIH GPP/IRTA Pre-doc Fellowship
University of Maryland Biophysics Graduate Program

Title: Balancing friendship networks while breaking up: Integrative network properties during avalanche homeostasis in nonhuman primates

Authors: *S. R. MILLER[1,2], S. YU[3], S. PAJEVIC[4], D. PLENZ[2]
[1]UMCP, Washington, DC; [2]Sect Critical Brain Dynamics, NIMH, Bethesda, MD; [3]Brainnetome Ctr., Inst. of Automation, Chinese Acad. of Sci., Beijing, China; [4]OIR/CIT, NIH, Bethesda, MD

Abstract: Cortical networks function robustly and reliably even while their internal configurations flexibly adapt to external environmental changes. Across many species, spontaneous and evoked neuronal activity in cortex has been found to be scale-invariant, termed ‘neuronal avalanches’. The scale-invariance dictates that avalanche sizes and durations obey fixed ratios over all spatiotemporal scales as quantified by power laws. Whether and how the cortex reconfigures internal connections while maintaining these fixed avalanche ratios is currently not known. Here, we specifically study 'friendship networks' (characterized by high neighborhood overlap between strongly connected nodes), which have been observed in the functional connectivity of many complex networks as well as cortex (Pajevic and Plenz, 2012). We followed neuronal avalanche dynamics over many days and weeks in premotor and prefrontal cortices of non-human primates (n = 3). The ongoing local field potential (LFP) was recorded with chronically implanted high-density multielectrode arrays for 20-60 min each day over successive weeks. Avalanches were defined as spatiotemporal clusters of negative, threshold-crossing LFP fluctuations on the array. We found that the power law in avalanche size, i.e. the number of threshold crossings within a cluster, was stable in each monkey and cortex area as was the mean pairwise correlation strength between local cortical sites. In contrast, individual pairwise correlations changed significantly over time, with highest changes observed in premotor cortex. Despite these changes, integrative 'friendship' network properties were maintained with regard to (1) robustness to weak-link pruning and (2) a positive correlation between excess clustering and link weights. This demonstrates that changes between two cortical

sites consistently alters their neighborhoods. We are currently exploring these network properties using parametric models with correlation matrices, i.e. functional connectivity derived from the mean and co-variance of experimentally obtained activity. Our results demonstrate avalanche homeostasis over many weeks in nonhuman primates in the face of changing pairwise correlations that preserve integrative network properties.

Disclosures: S.R. Miller: None. **S. Yu:** None. **S. Pajevic:** None. **D. Plenz:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.19/MMM23

Topic: I.07. Data Analysis and Statistics

Support: NIH 5 R01 MH110514-03
FISP 3-G3126
FISP 3-U3056

Title: Generalized linear model approach for predicting neural spiking activity from oscillatory phase

Authors: *T. D. JOHNSON[1], T. P. COLEMAN[2], L. M. RANGEL[1]
[1]Cognitive Sci., [2]Bioengineering, UCSD, LA Jolla, CA

Abstract: The synchronous ionic currents that give rise to neural oscillations have complex influences on neuronal spiking activity that are often challenging to characterize. Here we present an unbiased workflow using a generalized linear model (GLM) that characterizes the conditional probabilistic relationship between neural spiking activity and the instantaneous phase of a neural oscillation. Importantly, this workflow does not require any *a priori* knowledge of the distribution of spikes across the phases of an oscillation. The workflow generates a parametric point process GLM using an overcomplete basis of circular Von Mises functions in order to capture multi-modal aspects of spike-phase relationships that individual Von Mises function models cannot. It performs model-fitting with L1-regularized maximum likelihood, where selection of the regularizer coefficient is performed with model selection procedures (e.g. Akaike Information Criterion) to select the optimal penalty that enables the model to best capture spike-phase relationships without overfitting. We apply the time rescaling theorem to assess goodness of the fitted model and compare actual and theoretical spike distributions through Kolmogorov-Smirnov plots. This workflow is applied to synthetic data where it successfully characterizes spike-phase relationships. When applied to *in vivo* hippocampal data acquired from behaving rodents, the workflow robustly characterized a relationship between CA1 interneuron spiking and the instantaneous phase of the theta rhythm, a phenomenon that has been widely observed.

In addition, the workflow captures spiking relationships to faster rhythms (e.g. high gamma) nested within a slower rhythm (e.g. theta). In summary, the workflow advances the manner in which spike-phase relationships are both visualized and quantified, and can capture multi-modal spike-phase relationships, including coherence with multiple nested rhythms. As such, the workflow shows promise as a general-purpose tool for assessing the role that neural oscillations can have on the generation of spiking activity in neurons.

Disclosures: T.D. Johnson: None. **T.P. Coleman:** None. **L.M. Rangel:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.20/MMM24

Topic: I.07. Data Analysis and Statistics

Title: Interactive data visualization for electrophysiological data

Authors: *E. L. DENOVELLIS[1], E. P. STEPHEN[3], U. EDEN[1], M. A. KRAMER[2]
[1]Mathematics and Statistics, [2]Dept. of Mathematics and Statistics, Boston Univ., Boston, MA; [3]MIT, Cambridge, MA

Abstract: Functional network analysis is a growing area of neuroscience research, driven in part by technological improvements allowing us to record from more sensors simultaneously. However, as researchers record from more sensors, network analyses can become unwieldy and hard to interpret, because the number of possible network connections scales quadratically with the number of sensors (e.g. electrodes). Further, we expect neural processes to form dynamic networks that vary over time, frequency, and spatial scales (e.g. within and between brain regions), adding complexity to network analyses. While careful statistical modeling and strong hypotheses are important for yielding interpretable results, interactive visualizations are a neglected tool for coping with high-dimensional analyses. Visualizations allow us to make multiple simultaneous comparisons, easing the cognitive burden on working memory by efficiently encoding properties of the data into features salient to the visual system. Adding interactivity allows the user to change perspectives and modify analyses on demand, facilitating comprehension and hypothesis generation.
We present an interactive web-based visualization application, SpectraVis, that: (1) displays task-related functional networks over time and frequency, (2) compares individual and associative measures on sensor pairs (e.g. spectra, coherences), (3) compares different measures of association (e.g. correlation vs. coherence, binary vs. weighted networks), and (4) views networks at two spatial scales (sensor- and region-of-interest-level). The different modules of SpectraVis are dynamically linked, highlighting relationships between the metrics in response to user interaction. We demonstrate its capabilities on an electrocorticography dataset collected

during an overt reading task. Additionally, SpectraVis is open-source and free to use by the community. See https://github.com/NeurophysVis/SpectraVis

Disclosures: E.L. Denovellis: None. **E.P. Stephen:** None. **U. Eden:** None. **M.A. Kramer:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.21/MMM25

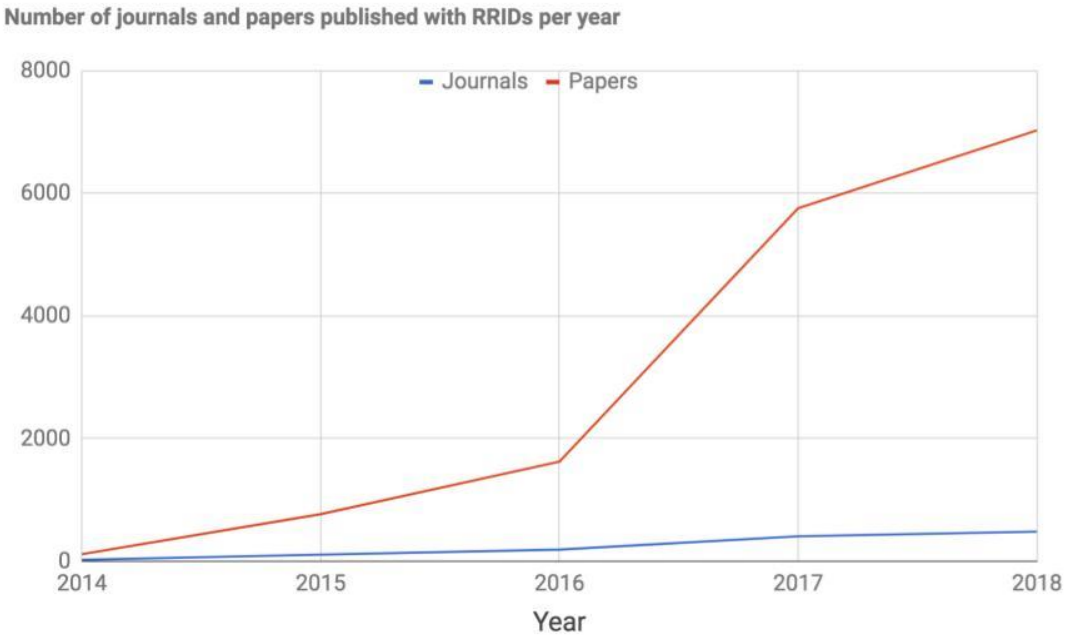
Topic: I.07. Data Analysis and Statistics

Support: R43OD024432

Title: RRIDs in the scientific literature, how can this help us all do better work?

Authors: *A. E. BANDROWSKI[1], Z. BABIC[2], M. E. MARTONE[3], J. S. GRETHE[2], E. VIETH[5], J. MENKE[1], I. FROMAN[1], R. VITA[2], T. GILLESPIE[4]
[1]UCSD, La Jolla, CA; [2]UCSD, San Diego, CA; [3]Neurosci., UCSD, La Jolla, CA; [4]Neurosci., UCSD, LA Jolla, CA; [5]SciCrunch, San Diego, CA

Abstract: RRIDs have proliferated in the scientific literature in the last three years leading to the need to create additional tools. How does the inclusion of RRIDs help? Readers of the paper with RRIDs are much more likely to find the reagents that authors used, making replication of parts of the paper easier. In 2016, we (Bandrowski et al) showed that being able to find an antibody in the Journal of Neuroscience before RRIDs was about 50% and after RRIDs was close to 90%. However, the use of RRIDs, now that this is more established is also capable of linking papers together based on the reagents they use. In SfN journals, the data about the RRID is also linked to the scicrunch resolver and links are visible that take readers to the information about the reagent, including a section where other papers that also use the reagent are described. The more RRIDs that are used, the richer this data set becomes, making it more likely that readers will be able to more easily find all of the reagents they are looking for and track down any problems with these reagents more easily. RRIDs are currently found in nearly 7000 scientific papers, and have been enforced in the Society for Neuroscience and Cell press journals since mid 2016. As of April 27, 2018, the Journal of Comparative Neurology has published 644 papers with RRIDs, the Journal of Neuroscience 604, Neuron 415, eLife 768, and eNeuro has published 158 papers. Altogether, 480 journals have at least one RRID.In order to keep up with the literature being released, current rate of papers is 13.3 per day, we have built automated tools to detect RRIDs and to make sure that papers that are published are added to the reagent records so that subsequent authors will see all the papers published which used the reagent.



Disclosures: **A.E. Bandrowski:** A. Employment/Salary (full or part-time):; SciCrunch Inc. **Z. Babic:** None. **M.E. Martone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch Inc. **J.S. Grethe:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch Inc. **E. Vieth:** None. **J. Menke:** None. **I. Froman:** None. **R. Vita:** None. **T. Gillespie:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.22/MMM26

Topic: I.07. Data Analysis and Statistics

Support: Xpansa

Title: Specifying PKC(x) isoform in different cellular location and anatomical locations of the cns based on the extracted knowledge

Authors: *Y. BUINITSKAYA[1], R. GURINOVICH[2], A. PASHUK[2], V. PUNTUS[1], A. DMITRIEVSKIY[2], A. SCERBACOV[2], Y. PETROVSKIY[2]
[1]sci.AI, Minsk, Belarus; [2]sci.AI, Tallinn, Estonia

Abstract: There are 70k+ papers mentioning PKC proteins family across the literature. Success and reproducibility of the new experiment involving PKC(x) strongly tied to reutilization of the knowledge about particular isoform in prior scientific report. It leads to different functional roles of the similar molecules. (Differentiation of the functions is reported in our adjacent poster "Inferring PKC(x) function in CNS Based on the Extracted Knowledge About Protein's Isoform").
Based on our upstream literature-based research of PKCs' role in pain mediating, we observed exceptional need to match cell and, in general, anatomical locations to identify specific PKCα, PKCγ, PKCε etc. isoforms. Locations hints present in sparse, distributed and, often, indirect, form in the macro context of the publication.
We utilize machine reasoning methods to discover possible models of biological processes and report clear feasibility to extract knowledge about particular PKC isoforms according to researcher's query.

Disclosures: Y. Buinitskaya: None. **R. Gurinovich:** None. **A. Pashuk:** None. **V. Puntus:** None. **A. Dmitrievskiy:** None. **A. Scerbacov:** None. **Y. Petrovskiy:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.23/MMM27

Topic: I.07. Data Analysis and Statistics

Support: HHSN276201700124P
R43OD024432

Title: RRIDs reduce the use of contaminated cell lines in scientific papers

Authors: *Z. BABIC[1], A. E. BANDROWSKI[2], M. E. MARTONE[3], J. S. GRETHE[4], T. GILLESPIE[5], B. OZYURT[2]
[1]UCSD, San Diego, CA; [3]Neurosci., [2]UCSD, La Jolla, CA; [4]UCSD, Poway, CA; [5]Neurosci., UCSD, LA Jolla, CA

Abstract: According to Capes-Davis et al (2010), reducing the prevalence of contaminated cell line use in papers requires significant vigilance on the part of journal editorial staff. The inclusion of Research Resource Identifiers, RRIDs, in contrast, requires that the author looks at the data entry for a cell line, which includes the information that the cell line is contaminated. We hypothesize that RRID inclusion impacts the prevalence of contaminated cell line in the absence of specific editorial oversight. The list of contaminated cell lines, their RRIDs and synonyms was obtained from the Cellosaurus database (April 1, 2018). RRIDs were noted by authors for 1,554 cell lines (686 papers), of which 52 in 47 papers were on the list of

contaminated cell lines, which constitutes 3.3% of cell lines in 6.9% of papers. The population of all papers that used cell lines was estimated based on the SciScore tool run across ~2M open access papers' methods sections (data was obtained from PubMed Central). Of these 305,161 unique cell line names (150,459 articles) were identified and contamination was estimated at 26,418 (8.6%), this corresponds to a rate of use of contaminated cell lines in 16.1% of papers, a number somewhat lower than previous estimates of 20% by experts using only PubMed Central and other search tools. To verify that SciScore recognized most cell lines, we tested 1,004 random Scientific Reports articles and manually annotated whether or authors used cell lines, then we compared results and found a concurrence of 95% between SciScore and our curator who was blinded to the SciScore results. Our results show that the rate of use of contaminated cell lines is significantly lower in RRID papers than in the average paper, thus we suspect that inclusion of RRIDs, without the need for direct editorial oversight or a specific workflow reduces the use of contaminated cell lines in papers.

Disclosures: Z. Babic: None. **A.E. Bandrowski:** A. Employment/Salary (full or part-time):; SciCrunch Inc.. **M.E. Martone:** None. **J.S. Grethe:** None. **T. Gillespie:** None. **B. Ozyurt:** A. Employment/Salary (full or part-time):; SciCrunch Inc..

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.24/MMM28

Topic: I.07. Data Analysis and Statistics

Support: NSF STC award CCF-1231216
Hampshire Culture Brain and Development grant
Sherman Fairchild grant

Title: An online platform for reproducible neural data analyses

Authors: *E. M. MEYERS[1], L. RITHICHOO[3], T. ZHANG, 01002[2], P. LU, 01002[2]
[1]Brain & Cognitive Sci., [2]Hampshire Col., Amherst, MA; [3]Mount Holyoke Col., South Hadley, MA

Abstract: As neuroscientists continue to collect larger datasets (Stevenson et al, 2011) new data tools are needed that can efficiently extract insights from this data (Brown et al, 2004). To continue to address this need, we have created an open source R implementation of the Neural Decoding Toolbox (Meyers 2013) that makes it easy to apply decoding analyses to neural data. Because the R programming language is widely used by Statisticians and Data Scientists, we hope that this package will encourage researchers from these communities to become more involved with analyzing neural data. Additionally, we have created an interactive online platform

where neuroscientists with no programming experience can apply decoding and other analyses through a web-based graphical user interface. The platform outputs a reproducible document that contains data analysis code along with the resulting figures, making it easy for researchers to reproduce and extend the results. We also aim to connect the platform to cloud based servers to allow drastic speedups in the time it takes to analyze data. Overall, these tools will make it significantly faster and easier to analyze neural data, which should increase the pace of discovery in neuroscience.

Disclosures: E.M. Meyers: None. **L. Rithichoo:** None. **T. Zhang:** None. **P. Lu:** None.

Poster

703. Neuronal Network Models Applied to Neuroscience

Location: SDCC Halls B-H

Time: Wednesday, November 7, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 703.25/MMM29

Topic: I.07. Data Analysis and Statistics

Support: HHMI
DARPA
NIH
Helen Hay Whitney Foundation

Title: Maximum likelihood and machine learning based methods for automated cell sorting of large-scale neural calcium imaging data

Authors: *B. AHANONU[1,2,3], L. J. KITCH[2], T. H. KIM[2], M. C. LARKIN[2], E. OTTO HAMEL[2], J. LECOQ[5], D. E. ALDARONDO[6], M. J. SCHNITZER[1,2,3,4]
[1]Dept. of Biol., [2]CNC Program, [3]Howard Hughes Med. Inst., [4]Dept. of Applied Physics, Stanford Univ., Stanford, CA; [5]Structured Sci., Allen Inst., Seattle, WA; [6]Neurosci., Princeton Univ., Princeton, NJ

Abstract: Recent advances in large-scale calcium imaging allow neuroscientists to visualize concurrently the dynamics of thousands of individual neurons in live animals, but analysis of these datasets remains a bottleneck. There are several existing algorithms for extracting individual cells and their calcium activity traces from the raw video data, yet no algorithm to date has demonstrated the requisite speed, scalability, accuracy, and versatility to provide a general solution. Here we present CELLMax (Cell Extraction by Log-Likelihood Maximization), a high-fidelity cell extraction method that makes no assumptions about the statistical structure of cell shapes or activity waveforms. CELLMax is highly parallelizable and its runtime scales favorably with dataset size. In validation studies on simulated and real datasets, CELLMax yielded activity traces of higher signal-to-noise ratio than those from other commonly used cell sorting methods. Neural activity traces extracted by CELLMax also enabled superior decoding of

neural ensemble signals. We further combined CELLMax with machine learning based classification approaches to distinguish actual neurons from other non-cellular signal sources in the calcium videos. This combination enabled fast and accurate cell identification when applied to one- and two-photon calcium imaging datasets acquired in multiple brain areas including neocortex, basal ganglia, hippocampus, and amygdala. Overall, our computational pipeline comprising CELLMax and automated signal source classification provides a versatile, reliable, parallelizable and scalable means of extracting cellular dynamics in a wide variety of calcium imaging studies. Thus, we expect its usage will improve the speed and accuracy of experiments relying on large-scale neural imaging.

Disclosures: B. Ahanonu: None. **L.J. Kitch:** None. **T.H. Kim:** None. **M.C. Larkin:** None. **E. Otto Hamel:** None. **J. Lecoq:** None. **D.E. Aldarondo:** None. **M.J. Schnitzer:** None.